
State of Palestine
Ministry of Health

# Chemotherapy Protocols 2013

# شكر وتقدير

تتقدم الإدارة العامة للصيدلة/وزارة الصحة الفلسطينية بالشكر والتقدير العميق لكافة من ساهم في إعداد هذا العمل القيم الذي يعد خطوة هامة على طريق ترشيد استعمال الأدوية في فلسطين للمساهمة في رفع المستوى الصحي.
هذا ونخص بالذكر معالي وزير الصحة الدكتور جواد عواد وعطوفة وكيل الوزارة الدكتور عنان المصري على دعمهم المستمر ومساندتهم لانجاز قائمة الأدوية الأساسية ،دليل الدواء الفلسطيني والبروتوكولات العلاجية.
كما نثمن عالياً المشاركة الفعالة للأطباء والصيادلة العاملين في وزارة الصحة الفلسطينية على ما بذلوه من جهد في إعداد ومراجعة هذا العمل الوطني الهام.
وأخيرا وليس أخرا نتقدم بالشكر والتقدير إلى الوكالة الفرنسية للتنمية وجامعة النجاح الوطنية اللذين لم يألوا جهداً في تقديم الدعم المادي والفني المتواصلين لإخراج هذا الدليل إلى النور.

**رانية شاهين**
**مدير عام الصيدلة**


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Rania Shaheen
General Director Of Pharmacy

## مقدمة

لقد استغرق العمل في إنجاز هذا الكتاب شهور من العمل الدؤوب والمناقشات والمحاضرات بين العاملين في مشروع ترشيد استهلاك الأدوية في جامعة النجاح الوطنية والزملاء في وزارة الصحة الفلسطينية. لقد قمنا وبالتنسيق الكامل مع وزارة الصحة الفلسطينية بإختيار قائمة مكونة من ١٢ بروتوكول علاجي حتى يتم تطويرها وتوزيعها ونشرها بين العاملين في القطاع الصحي في وزارة الصحة الفلسطينية. بالإضافة إلى ذلك، قمنا بمراجعة البروتوكولات العلاجية الخاصة بالأورام والتي تم نشرها من وزارة الصحة الفلسطينية عام ٢٠٠٨.

لقد تم تطوير هذه البروتوكولات بناء على المستجدات العلمية المنشورة وبناء على قائمة الأدوية ألأساسية الخاصة بوزارة الصحة ٢٠١٣. ولقد تم هذا العمل من خلال ورشات العمل المكثفة والتي تم فيها تقديم البروتوكولات للأطباء والصيادلة من وزارة الصحة من خلال محاضرات ونقاش في جامعة النجاح الوطنية وتبع ذلك سلسلة محاضرات على مستوى الوطن سواء كان ذلك في المستشفيات أو في مراكز الرعاية الأولية.

إن وجود بروتوكولات علاجية هو إحدى سمات العمل الصحي العلمي والذي سيؤدي حتما الى ترشيد استهلاك الأدوية وذلك من خلال تقنين استعمال الأدوية المبنية على البروتوكول العلاجي. ولقد شملت البروتوكولات مجموعة من الأمراض الشائعة وكيفية علاجها وكيفية التأقلم في العلاج مع القائمة الأساسية. إن البروتوكولات العلاجية وخاصة بروتوكولات الأورام ستعمل على ترشيد استهلاك الأدوية وتخفيض النفقات في حال تطبيقها حيث أن جزء كبير من ميزانية الأدوية قد يصل إلى ٣٠٪ يتم صرفة لأدوية السرطان.

إن هذه البروتوكولات هي بداية عمل قابل للتطور مع الوقت وأني أوجه دعوة للزملاء العاملين في القطاع الصحي للمساعدة في تطوير بروتوكولات علاجية لجميع الأمراض وتوحيدها بين جميع العاملين في فلسطين علما بأن هذا النقاش والتطور هو ضروري جدا ولمصلحة الجميع بمن فيهم الإنسان الفلسطيني.

# شكر وتقدير

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# Chapter 1

# SOLID TUMORS

Chapter 1

# BREAST CANCER

## AC (doxorubicin, Cyclophosphamide)

## Indications:

- Neoadjuvant / adjuvant chemotherapy for operable and invasive breast cancer.
- Palliative therapy in patients with advanced breast cancer, if no prior anthracycline exposure.

### AC schedule

●=i.v.

| Day | 1 | every 21 days cycle for four cycles |
|---|---|---|
| Doxorubicin, 60 mg/m² i.v. | ● | |
| Cyclophosphamide, 600 mg/m² i.v. | ● | |
| Followed by paclitaxel 80 mg/m² by 1 hr IV infusion weekly for 12 weeks | | |

### OR

| Day | 1 | every 14 days cycle for four cycles |
|---|---|---|
| Doxorubicin, 60 mg/m² i.v. | ● | |
| Cyclophosphamide, 600 mg/m² i.v. | ● | |
| Followed by paclitaxel 175 mg/m² by 3 hrs IV infusion day 1 | | |
| All cycles are with filgrastim support | | |

### OR

| Day | 1 | every 21 days cycle for four cycles |
|---|---|---|
| Doxorubicin, 60 mg/m² i.v. | ● | |
| Cyclophosphamide, 600 mg/m² i.v. | ● | |
| Without being followed with paclitaxel | | |

## Refrences:


1. National Comprehensive Cancer Network 2012.
2. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial [1]. Biganzoli, L., et al., Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. J Clin Oncol, 2002. 20(14): p. 3114-21.
3. Evans TR et al. Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an Anglo-Celtic cooperative oncology group study. J. Clin. Oncol. 23 (2005): 2988-2995.

4. Fisher B et al. Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-25. J. Clin. 17 (1999): 3374-3388.
5. Goldstein LJ et al. Concurrent doxorubicin plus doctaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E 2197. J. Clin, 26 (2008): 4092-4099.
6. Jones RL et al. A randomized pilot phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. Br. J. Cancer 100 (2009): 305-310.
7. Henderson IC et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J. Clin. Oncol. 21 (2003): 1431-1439.
8. Loesch D et al. Phase III multicenter trial of doxorubicin plus cyclophosphamide followed by paclitaxel as adjuvant therapy for women with high-risk breast cancer. J. Clin. Oncol. 28 (2010): 2958-2965.
9. Sparano JA et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N. Engl. J. Med. 358 (2008): 1663-1671.
10. Journal of Clinical Oncology 2010.
11. Pharmacotherapy: A Pathophysiologic Approach, 8th Edition (December) [2].

# Capecitabine + Docetaxel

## Indications:

- In combination with docetaxel for patients with locally advanced or metastatic breast cancer after failure of anthracycline containing chemotherapy.

**Capecitabine schedule** **o=p.o**

| Day | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 | 3-week cycle<br>Until disease progression o or<br>Unacceptable toxicity |
|---|---|---|
| **Capecitabine,**<br>1000-1250 mg/m² b.d | o o o oo oo oo o o o o o | |
| Docetaxel | 75mg/m²1 h i.v. inf | d1 |

## OR

| D | Drug | Do, mg/m² | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1-14 | Capecitabine | 2000-2500 | ----- | ----- | ----- | PO |
| 1 | Docetaxel | 75-100 | 0.9% NaCl | 250 | 1 hr | IV |

| Day | Capecitabine (Day 1-14)<br>Docetaxel (Day 1)<br>Day 1 | Capecitabine (Day 1-14)<br>Docetaxel (Day 1)<br>Day 22 |
|---|---|---|
| | 1----------14----------22----------36---------- | |
| Cycle | 1 | 2 |

## References:


12. O'Shaughnessy J. et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: pahse II trial results. J. Clin. Oncol. 20 (2002): 2812-2823.
13. National Comprehensive Cancer Network 2012.
14. Journal of Clinical Oncology 2002.

# AT (Docetaxel– Doxorubicin) or (Epirubicin/ Docetaxel)

## Indications:

- Neoadjuvant/Adjuvant chemotherapy for invasive breast cancer.
- First line metastatic breast cancer
- Early breast cancer

## AT schedule

Doxorubicin 50 mg/m² i.v. once, day 1 followed after 1 hour by
Docetaxel 75 mg/m² i.v. infusion 1h day1
To be repeated every 3 weeks

| D | Drug | Do, mg/m² | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Epirubicin | 75 | 0.9% NaCl | 500 | 1 hr | IV |
| 1 | Docetaxel | 75 | 0.9% NaCl | 250 | 1 hr | IV |
| To be repeated every 21 days. | | | | | | |

| Day | Epirubicin<br>Docetaxel<br>Day 1 | Epirubicin<br>Docetaxel<br>Day 22 |
|---|---|---|
| | 1----------22---------- | |
| Cycle | 1 | 2 |

## References:


1. National Comprehensive Cancer Network 2012.
2. Bontenbal M et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the clinical Trial Group of the Comprehensive Cancer Centre. J. Clin. Oncol. 23 (2005): 7081-7088.
3. Nabholtz JM et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J. Clin. Oncol. 21 (2003): 968-975.
4. Journal of Clinical Oncology 2004+2005.
5. Bonneterre J., Br J Cancer 91: 1466ff; 2004.

# CMF (Cyclophosphamide-Methotrexate-5-fluorouracil)

## Indications:

- Adjuvant chemotherapy for operable and metastatic breast cancer not suitable for anthracyclines.

**CMF schedule** ●=i.v. o=p.o

| Day | 1 | 8 | Repeat cycle every 21 days for 6 cycles |
|---|---|---|---|
| Cyclophosphamide, 600 mg/m² | * | | |
| Methotrexate, 40 mg/m²i.v. (max 50 mg) | ● | * | |
| 5-FU, 600mg/ m² | ● | • | i.v. (max 1 mg) |

**OR**

| D | Drug | Do, mg/m² | R |
|---|---|---|---|
| 1-14 | Cyclophosphamide | 100 | PO |
| 1+8 | Methotrexate | 40 | IV |
| 1+8 | 5-Fluorouracil | 600 | IV |
| Repeat cycles every 21 days for six cycles. | | | |

**OR**

| D | Drug | Do, mg/m² | R |
|---|---|---|---|
| 1 | Cyclophosphamide | 600 | IV |
| 1 | Methotrexate | 40 | IV |
| 1 | 5-Fluorouracil | 600 | IV |
| Repeat cycles every 21 days for eight cycles. Followed by: | | | |
| 1 | Doxorubicin | 75 | IV |
| To be repeated every 3 weeks (4 cycles) as adjuvant chemotherapy for patients with HER2+ tumors. | | | |

## References:


1. National Comprehensive Cancer Network 2012.
2. Engelsman E et al. “Classical” CMF versus a 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer. An EORTC Breast Cancer Co-operative Group phase III trial (10808). Eur. J. Cancer 27 (1991): 966-970.
3. Coldhirsch A et al. Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? Ann. Oncol. 9 (1998): 489-493.
4. Moliterni A et al. HER2 over expression and doxorubicin in adjuvant chemotherapy for resectable breast cancer. J. Clin. Oncol. 21 (2003): 458-462.
5. Journal of Clinical Oncology 2003.

# Docetaxel

## Indications:

- Palliative therapy in patients with advanced breast cancer resistant to anthracyclines or previously exposed to anthracyclines in the adjuvant setting.
- Chemotherapy for recurrent or metastatic breast cancer.
- Adjuvant chemotherapy for high risk patients and lymph node positive patients.

**Docetaxel schedule** ●=i.v.

| Day | 1 | 3-week cycle for 6 cycles |
|---|---|---|
| Docetaxel, 60-100 mg/m² i.v. infused over 1 hour ● | | |

| D | Drug | Do, mg/m² | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Docetaxel | 60-100 | 0.9% NaCl | 250 | 1 hr | IV |
| ● To be repeated every 21 days for 6 cycles. | | | | | | |

| Day | Docetaxel Day 1 | Docetaxel Day 22 |
|---|---|---|
| | 1----------22---------- | |
| Cycle | 1 | 2 |

## OR

**Docetaxel schedule:**

- Docetaxel 35-40 mg/m², I.V. (1 hr inf) weekly.
- Each cycle consisted of 3 weeks of therapy followed by 1 week of rest or 6 weeks of therapy followed by a 2-week treatment break.

## References:


1. National Comprehensive Cancer Network 2012.
2. Chan S et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J. Clin. Oncol. 17 (1999): 2341-2354.
3. Harvey V et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J. Clin. Oncol. 24(2006): 4963-4970.
4. Jones SE et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.J. Clin. Oncol. 23(2005): 5542-5551.
5. Journal of Clinical Oncology 1999 + 2005 + 2006.
6. Burestin HJ et al. Docetaxel administered on a weekly basis for metastatic breast cancer. J. Oncol. 18 (2000): 1212-1219.
7. Rivera E et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer 112

(2008): 1455-1461.

8. Yardley DA et al. A phase II randomized crossover study of liposomal doxorubicin versus weekly docetaxel in the first-line treatment of women with metastatic breast cancer. Clin. Breast Cancer 9 (2009): 247-252.

# FEC (5-fluorouracil-epirubicin-cyclophosphamide)

## Indications:

- Neoadjuvant/ adjuvant chemotherapy for operated breast cancer
- Palliative therapy in patients with advanced breast cancer if no previous anthracyclines therapy.

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Cyclophosphamide | 500-600 | 0.9% NaCl | 500 | 60’ | IV |
| 1 | Epirubicin | 50-100 | 0.9% NaCl | 250 | 30’ | IV |
| 1 | 5-Fluorouracil | 500-600 | 0.9% NaCl | 100 | 20’ | IV |
| To be repeated every 3 weeks (or as dose-dense therapy every 2 weeks with G-CSF support). | | | | | | |

| Day | Cyclophosphamide/ Epirubicin/ 5-Fluorouracil Day 1 | Cyclophosphamide/ Epirubicin/ 5-Fluorouracil Day 22 |
|---|---|---|
| | 1----------22---------- | |
| Cycle | 1 | 2 |

## References:


1. National Comprehensive Cancer Network 2012.
2. Bonneterre J et al. Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French Adjuvant Study Group 05 randomized trial. J. Clin. Oncol. 23(2005): 2686-2693.
3. Ejlertsen B et al. Improved outcome from substituting methotrexate with epirubicin: results from a randomized comparison of CMF versus CEF in patients with primary breast cancer. Eur. J. Cancer 43(2007):877-884.
4. Ellis P et al; TACT Trial Management Group; TACT Trialists. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT); an open-label, phase III, randomized controlled trail, Lancet 373 (2009): 1681-1692.
5. French Epirubicin Study Group. Epirubicin-based chemotherapy in metastatic breast cancer patients: Role of dose-intensity and duration of treatment. J. Clin. Oncol. 18 (2000): 3115-3124.
6. Sirohi B et al. A randomized comparative trial of infusion ECisF versus conventional FEC as adjuvant chemotherapy in early breast cancer: the TRAFIC trial. Ann. Oncol. 21 (2010): 1623-1629.
7. Van der Hage JA et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and treatment of cancer trial 10902. J. Clin. Oncol. 19 (2001): 4224-4237.
8. Venturini M et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. J. Natl. Cancer inst. 97 (2005): 1724-1733.

# FAC (5-Fluorouracil-Doxorubicin-Cyclophosphamide)

## Indications:

- Neoadjuvant/ adjuvant chemotherapy for operated breast cancer
- Palliative therapy in patients with advanced breast cancer if no previous anthracyclines therapy.

## FAC Schedule:

- 5-FU 500 mg/$m^2$ I.V. day 1
- Doxorubicin 50 mg/$m^2$ I.V. day 1
- Cyclophosphamide 500 mg/$m^2$ I.V. day 1
- To be repeated every 3 weeks.

## Paclitaxel

## Indications:

- Palliative therapy in patients with advanced breast cancer resistant to anthracyclines or previously exposed to anthracyclines in the adjuvant setting.
- Adjuvant chemotherapy for breast cancer.
- First-line therapy for metastatic breast cancer.

**Paclitaxel schedule** **●=i.v.**

| Day | 1 | | | | 3-week cycle for 6 cycles |
|---|---|---|---|---|---|
| Paclitaxel, 175 mg/ m² i.v | ● | | | | infused over 3 hour |

**OR**

| Day | 1 | 8 | 15 | 4-week cycle |
|---|---|---|---|---|
| Paclitaxel, 80 mg/ m² i.v, infused over 1 hour | ● | | ● | ● |

# Vinorelbine

## Indications:

- Palliative therapy in patients with advanced breast cancer previously treated or not suitable for anthracyclines and or taxanes.
- Adjuvant chemotherapy for breast cancer.
- Preferred chemotherapy for recurrent or metastatic breast cancer, first-line agent for HER2-positive disease.

| **Vinorelbine schedule** | | | **●=i.v.** |
|---|---|---|---|
| Day | 1 | 8 | 4-week cycle for 6 cycles |
| Vinorelbine, 25-30 mg/ m² i.v given | ● | ● | over 6-10 minutes (maximum 60mg) |

# Vinorelbine + Capecitabine

## Indications:

- Palliative therapy in patients with advanced breast cancer.
- Adjuvant chemotherapy for breast cancer.

## Vinorelbine + Capecitabine schedule:

- Capecitabine 1000 mg/m$^2$ P.O. b.i.d. on days 1-14.
- Vinorelbine 25 mg/m$^2$ I.V. on days 1 and 8
- To be repeated every 21 days.

# References:

1. Welt A. Ann Oncol. 2005; 16: 64-69.

# TC (Docetaxel + cyclophosphamide)

## Indications:

- Neoadjuvant/ adjuvant chemotherapy for breast cancer

## Schedule:

- Docetaxel 75 mg/$m^2$ IV (30-60 min inf.), day 1
- Cyclophosphamide 600 mg/$m^2$ IV (30-60 min inf.), day 1
- To be repeated every 21 days for 4 cycles
- All cycles are with filgrastim support

# References:

1. National Comprehensive Cancer Network 2012.
2. Jones S et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 97353. J. Clin. Oncol. 27 (2009): 1177-1183.
3. Jones SE et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J. Clin. 24 (2006): 5381-5387.

# Hormonotherapy in Breast Cancer

One of the following:

- Letrozole 2.5 mg P.O. daily.
- Tamoxifen usually 20 mg P.O. daily.

## References:


1. National Comprehensive Cancer Network 2012.
2. Milla-Santos A et al. Anastrazole versus tamoxifen as first-line therapy in post-menopausal patients with hormone-dependent advanced breast cancer. A prospective, randomized, phase III study.Am. J. Clin. Oncol. (CCT) 26 (2003): 317-322.
3. Nabholtz JM et al. Anastrazole (Arimidex TM) versus tamoxifen as first-line therapy for advanced breast cancer in postmenpausal women: Survival analysis and updated safety results. Eur. J. Cancer 39 (2003): 1684-1689.
4. BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N. Engl. J. Med. 361 (2009): 766-776.
5. Alkner S et al; South Swedish and South-East Swedish Breast Cancer Groups. Tamoxifen reduces the risk of contralateral breast cancer in premenopausal women: Results from a controlled randomized trial. Eur. J. Cancer 45 (2009): 2496-2502.

# TAC (Doxorubicin – Cyclophosphamide – Docetaxel)

## Indications:

- First line metastatic breast cancer
- Early breast cancer

| TAC schedule | | | | | | ●=i.v |
|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 3-week cycle for 6 cycles |
| Doxorubicin 50 mg/m² i.v b. | ● | | | | | followed immediately by |
| Cyclophosphamide 500 mg/m² i.v b. | ● | | | and then after completion of Doxorubicin inf. | | |
| Docetaxel 75 mg/m²i.v, inf. | ● 1 h | | | | | |

(Doxorubicin should be given first).

Repeat cycles every 21 days for six cycles (must be given with growth factor support)

## Gemcitabine Monotherapy

## Indications:

- Metastatic breast cancer

## Gemcitabine schedule:

- Gemcitabine 1200 mg/m² I.V. (30 min inf) on day 1, 8, and 15.
- To be repeated every 4 weeks.
- OR
- Gemcitabine 1250 mg/m² I.V. day 1+8.
- To be repeated every 3 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Spielmann M. et al. Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology 60 (2001): 303-307.
3. Suzuki Y et al. Phase II study of gemcitabine monotherapy as a salvage treatment for Japanese metastatic breast cancer patients after anthracycline and taxane treatment. J. Jpn. J. Clin. Oncol. 39 (2009): 699-706.

# BLADDER CANCER

## 1. Deep Muscle Bladder Cancer
## CMV (Cisplatin – Methotrexate – Vinblastine)

### Indications:

- Palliative therapy in metastatic bladder cancer.
- Neoadjuvant therapy in muscle-invasive transitional cell bladder cancer.

**CMV Schedule** ● = i.v.

| Day | 1 | 2 | 8 | 3-week cycle |
|---|---|---|---|---|
| Methotrexate, 30 mg/m² i.v. | ● | | ● | |
| Vinblastine, 4 mg/m² i.v. | ● | | ● | |
| Cisplatin, 100 mg/m² i.v. infusion | | ● | | |

## Gemcitabine – Cisplatin (First-Line)

### Indications:

- First-line chemotherapy (neoadjuvant/ adjuvant/ metastatic) bladder cancer.
- Palliative therapy in metastatic bladder cancer.

**Gemcitabine – cisplatin schedule** **●=i.v.**

| Day | 1 | 2 | 8 | 15 | 4-week cycle |
|---|---|---|---|---|---|
| Gemcitabine, 1000 mg/m² i.v. infusion | ● | | ● | ● | |
| Cisplatin, 70 mg/m² i.v. infusion | | ● | | | |

### References:

1. National Comprehensive Cancer Network 2012.
2. Von der Maase H., J clin Oncol 18 (17): 3068ff, 2000.

# MVAC (Methotrexate-Vinblastine-Doxorubicin*-Cisplatin) (first line)

## Indications:

- First-line chemotherapy (neoadjuvant/ adjuvant/ metastatic) bladder cancer.
- Palliative therapy in metastatic bladder cancer.
- Neoadjuvant therapy in muscle-invasive transitional cell bladder cancer.
- Adjuvant therapy in resected muscle transitional cell bladder cancer.

| **MVAC schedule** | | | | **●=i.v.** |
|---|---|---|---|---|
| Day | 1 | 15 | 22 | 4-week cycle |
| Methotrexate, 30 mg/m² i.v. | ● | ● | ● | |
| Vinblastine, 3 mg/m² i.v. | ● | ● | ● | |
| Doxorubicin, 30 mg/m² i.v. | ● | | | |
| Cisplatin, 70 mg/m² i.v. infusion | ● | | | |

**OR**

Accelerated MVAC schedule

| D | Drug | Do, mg/m$^2$ | R |
|---|---|---|---|
| 1 | Methotrexate | 30 | IV |
| 2 | Vinblastine | 3 | IV |
| 2 | Doxorubicin | 30 | IV |
| 2 | Cisplatin | 70 | IV (infusion) |
| 2-week cycle<br>G-CSF is given subcutaneously on days 4-11 of each cycle | | | |

## References:

1. National Comprehensive Cancer Network 2012.
2. Sternberg CN, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin, for advanced transitional cell carcinoma of the urothelium. Efficacy abd patterns of response and relapse. Canser 1989; 64: 2448-2458.

## 2. Superficial Bladder Cancer

### BCG immunotherapy

### Indications:

- For prophylaxis or recurrence and progression after surgery

### Schedule

BCG immunotherapy, 81 mg intravesically weekly for 6 weeks

### Mitomycin C

### Indications:

- Superficial bladder cancer

### Schedule

Mitomycin C 30-40 mg intravesically weekly × 4-6 weeks then monthly × 6 months

# GASTROINTESTINAL CANCER

## ANAL CANCER

### 1. Localaized Anal Cancer
### Mitomycin C, 5-fluorouracil + Radiotherapy

### Indications:

- Combines with radiotherapy in anal cancer.

| **Mitomycin C, 5-FU schedule** | | | | | | **●=i.v.** |
|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 24-25-26-27-28 |
| Mitomycin C, 12 mg/ m² i.v | ● | | | | | |
| 5-FU.1000mg// m², 24-hour infusion | ● | ● | ● | ● | * | * * * * * |
| **OR** | | | | | | |
| Mitomycin C, 12 mg/ m² i.v | ● | | | | | |
| 5-FU.750mg/m², 24-hour infusion | ● | ● | ● | ● | ● | * * * * * |
| week 5 Repeat 5-FU schedule, no mitomycin C | | | | | | |

**Repetition:** none

5 FU by continuous infusion during the first and final weeks of radiotherapy.

**OR**

- 5-FU 750 mg/m$^2$ I.V. (cont. inf), days 1-5 **or** 1000 mg/m$^2$ I.V. (cont. inf), days 1-4.
- Mitomycin 10-15 mg/m$^2$ I.V., day 1
- Concomitant with radiotherapy
- To be repeated after 4 weeks.

### References:


1. National Comprehensive Cancer Network 2012.
2. Ajani JA et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. A randomized controlled trial. JAMA 299 (2008): 1914-1921.
3. Bartelink H et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J. Clin. Oncol. 15 (1997): 2040-2049.
4. Novothover J et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomized UKCCCR Anal Cancer Trial (ACT I). Br. J. Cancer 102 (2010): 1123-1128.

# 2. Metastatic Anal Cancer

## 5-FU + Cisplatin + RT

- Continuous infusion 5-FU 1000 mg/m$^2$/day; IV days 1-5
- Cisplatin 100 mg/m$^2$; IV day 2
- Repeat every 4 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Hung A et al. Cisplatin-based combined modality therapy for anal carcinoma. A wider therapeutic index. Cancer 97 (2003): 1195-1202.

# COLORECTAL CANCER

## Capecitabine

## Indications:

- First – line metastatic colorectal cancer
- Adjuvant chemotherapy for colorectal cancer

**Capecitabine schedule**

Capecitabine 1000-1250 mg/ m², PO twice daily for 14 days in a 21-day cycle for 8 cycles (as adjuvant therapy) over 24 weeks and 10 cycles (for metastatic colorectal cancer).

## References:


1. National Comprehensive Cancer Network 2012.
2. Cassidy J et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann. Oncol. 13 (2002): 566-575.
3. Feliu ST et al. Capecitabine as first-line treatment for patients older than 70 years with metastatic colorectal cancer: an Oncopaz cooperative group study. J. Clin. Ocnol. 23 (2005): 3104-3111.
4. Kim ST et al. Capecitabine monotherapy as salvage treatment after failure of chemotherapy containing oxaliplatin and irinotecan in patients with metastatic colorectal cancer. Asia Pac. J. Clin. Oncol. 7 (2011): 82-87.
5. Twelves C et al. Capecitabine as adjuvant treatment for stage III colon cancer. N. Engl. J. Med. 352 (2005): 2696-2704.

# De Gramont (Leucovorin-5-Fluorouracil) First choice

## Indications:

- Palliative treatment metastatic colorectal carcinoma
- Adjuvant treatment of colorectal cancer

**De Gramont schedule** **●=i.v.**

| Day | 1 | 2 | 15 | 16 | Repetition every 29 days for 6 cycles |
|---|---|---|---|---|---|
| Folinic acid 200mg/m², 2-hour infusion | ● | ● | * | * | |
| 5-FU, 400mg/m², bolus | ● | ● | * | * | |
| 5-FU, 600mg/ m² 22-hour continuous infusion | ● | * | * | * | |

| D | Drug | Do, mg/m² | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1, 2, 15, 16 | Leucovorin | 200 | 0.9 % NaCl | 250 | 120 min | IV |
| 1, 2, 15, 16 | 5-FU | 400 | ------ | ------ | Bolus | IV |
| 1, 2, 15, 16 | 5-FU | 600 | 0.9 % NaCl | 500 | 22 hr | IV |

| Day | Leucovorin + 5-FU Day 1+2+15+16 | Leucovorin + 5-FU Day 29+30+43+44 |
|---|---|---|
| | 1+2----------15+16----------29+30----------43+44---------- | |
| Cycle | 1 | 2 |

## References:


1. National Comprehensive Cancer Network 2012.
2. Pharmacotherapy: A Pathophysiologic Approach, 8th Edition (December) [2].
3. De Gramont A. et al., J Clin Oncol 15: 808ff, 1997.
4. Andre T et al. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: Fianl results of GERCOR C96. 1. J. Clin. Oncol. 25 (2007): 3732-3738.
5. Ducreux M et al; FFCD 9601 Collaborative Group. Randomized trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Feferation Francophone de Cancerologie Digestive (FFCD) 9601 trial. Oncology 70 (2006): 222-230.
6. Ychou M et al. A phase III randomized trial of LV5FU2 + irinotecan ver-

sus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/ FFCD9802). Ann. Oncol. 20 (2009): 674-680.

# Mayo Clinic regimen

## 5- Fluorouracil – Folinic acid

## Indications:

- Adjuvant therapy for Dukes' stage B2, B3 and C cancer or the colon and rectum
- Palliative treatment metastatic colorectal carcinoma
- As a radio-sensitizer given concurrently with postoperative radiotherapy for cancer of the rectum.

**5- Folinic acid (LV) schedule** **●=i.v.**

| Day | 1 | 2 | 3 | 4 | 5 | Repeat every 4 to 5 week cycle (6 courses) |
|---|---|---|---|---|---|---|
| Folinic acid 20mg/m²/day; | ● | ● | ● | ● | ● | |
| IV days 1-5, (given first) | | | | | | |
| 5-FU,425mg/m²/day; IV days 1-5 | ● | ● | ● | ● | ● | when given with radiotherapy |
| To be repeated every 4 – 5 weeks. | | | | | | |

## References:

1. National Comprehensive Cancer Network 2012.
2. Pharmacotherapy: A Pathophysiologic Approach, 8th Edition (December).
3. Buroker TR et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J. Clin. Oncol. 12 (1994): 14-20.
4. Poon MA et al. Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J. Clin. Oncol. 9 (1991): 1967-1972.

# Oxaliplatin, 5- Fluorouracil, Folinic acid (FOLFOX 4)

## Indications:

- First-line metastatic or advanced disease
- Adjuvant therapy for operated colorectal cancer

**Oxaliplatin, 5- fluorouracil, folinic acid schedule** **●=i.v.**

| Day | 1 | 2 | 4-week cycle (6 courses) |
|---|---|---|---|
| Oxaliplatin, 85mg/m²; IV over 2-hour infusion day 1 | ● | | |
| 5-FU, 400mg/m², IV bolus after folinic acid | ● | ● | Repeat every 14 days |
| 5-FU, 600mg/m², 22-hour continuous infusion day 1 and 2 | ● | ● | Repeat every 14 days |
| Folinic acid 200 mg/m²/day, IV infusion over 2 hours; days 1 and 2 | ● | ● | |

| D | Drug | Do, mg/m² | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1, 15 | Oxaliplatin | 85 | 5% Glucose | 500 | 2 hr | IV |
| 1, 2, 15, 16 | Leucovorin | 200 | 0.9 % NaCl | 250 | 120 min | IV |
| 1, 2, 15, 16 | 5-FU | 400 | ------ | ------ | Bolus | IV |
| 1, 2, 15, 16 | 5-FU | 600 | 0.9 % NaCl | 500 | 22 hr | IV |

| Day | Oxaliplatin (Day 1+15)<br>Leucovorin + 5-FU (Day 1+2+15+16) | Oxaliplatin (Day 29+43)<br>Leucovorin + 5-FU (Day 29+30+43+44) |
|---|---|---|
| Cycle | 1 | 2 |

- Repetition every 29 days for 6 cycles.
- (*) Leucovorin as a modulator of 5-FU should always be administered before 5-FU.

## References:

1. National Comprehensive Cancer Network 2012.
2. Pharmacotherapy: A Pathophysiologic Approach, 8th Edition (December).
3. Alberts SR et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: A North Central Cancer Treatment Group phase II study. J. Clin. Oncol. 23 (2005): 9243-9249.

4. Andre T et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. J. Med. 350 (2004): 2343-2351.
5. Colucci G et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'ltalia Meridionale. J. Clin. Oncol. 23 (2005): 4866-4875.
6. Goldberg RM et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. J. Clin. Oncol. 24 (2006): 3347-3353.

# Oxaliplatin, 5- Fluorouracil, Folinic acid (FOLFOX 6)

## Indications:

- First-line metastatic or advanced disease
- Adjuvant therapy for operated colorectal cancer

## Oxaliplatin, 5- Fluorouracil, Folinic acid schedule

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1, 15 | Oxaliplatin | 100 | 5% Glucose | 500 | 2 hr | IV |
| 1, 15 | Leucovorin (*) | 400 | 0.9 % NaCl | 250 | 2 hr | IV |
| 1, 15 | 5-FU | 400 | ------ | ------ | Bolus | IV |
| 1, 15 | 5-FU | 2400 | 0.9 % NaCl | 500 | 44 hr | IV |

- To be repeated every 29 days for 6 cycles.
- (*) Leucovorin as a modulator of 5-FU should always be administered before 5-FU.
- 5-FU can be delivered via a pump in an outpatient setting.

## References:

1. National Comprehensive Cancer Network 2012.
2. Kato K et al. A multicenter phase-II study of 5-FU leucovorin and oxaliplatin (FOLFOX 6) in patients with pretreated metastatic colorectal cancer. Jpn. J. Clin. Oncol. 41 (2011): 63-68.
3. Tournigand C et al. FOLFIRI followed by FOLFOX 6 or the reverse sequnence in advanced colorectal cancer: a randomized GERCOR study. J. Clin. Oncol. 22 (2004): 229-237.

# CapeOX Protocol (Capecitabine + Oxaliplatin)

## Indications:

- Adjuvant therapy for colorectal cancer.

## CapeOX schedule:

- Oxaliplatin 130 mg/m$^2$ over 2 hours, day 1.
- Capecitabine 1000 mg/m$^2$ twice daily, days 1-14
- Every 3 weeks (for 24 weeks in adjuvant cases).

## References:

1. National Comprehensive Cancer Network 2012.
2. Schmoll HJ, Catwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007; 25: 102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared with Fluorouracil and Folinic Acid As Adjuvant Therapy foe Stage III Colon Cancer. J Clin Oncol 2011; 29: 1465-1471.

# GASTRIC AND ESOPHAGEAL CANCER

## ECF (Epirubicin, Cisplatin, 5-Fluorouracil)

## Indications:

- Perioperative chemotherapy; only for adenocarcinoma of the distal esophagus or esophagogastric junction.
- Metastatic cancer.

| **ECF schedule** | | | **●=i.v.** |
|---|---|---|---|
| Day | 1 | | |
| Epirubicin, 50 mg/m$^2$, i.v. | ● | 3-week cycle | |
| Cisplatin, 60 mg/m$^2$, i.v.infusion. | ● | | 3-week cycle |
| 5-FU, 200 mg/m$^2$/day; i.v.24-hour continuous infusion for 18-24 weeks (~21 weeks) | | | |

# Docetaxel + Cisplatin + 5 – FU (first Line therapy)

## Indications:

- For metastatic or locally advanced gastric cancer

| **Schedule** | | | | | | **●=i.v.** |
|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 3-week cycle |
| Docetaxel 75 mg/m² i.v, | ● | | | | | |
| Infusion on day 1 | | | | | | |
| Cisplatin 75 mg/m² i.v, | ● | | | | | |
| Infusion over 1-3 hours day 1 | | | | | | |
| 5-FU 750 mg/m²/day | ● | ● | ● | ● | ● | |
| Continuous i.v. infusion on days 1-5 | | | | | | |

# Docetaxel + Cisplatin (Fitrst-Line)

## Indicatios:

- Treatment of metastatic or locally advanced esophageal or esophagogastric cancers.

## Schedule

- Docetaxel 70-85 mg/m$^2$ IV on day 1
- Cisplatin 70-75 mg/m$^2$ IV on day 1

Repeat cycle every 21 days.

## References:


1. National Comprehensive Cancer Network 2012.
2. Roth AD, Fazio N, Stuupp R, et al. Docetaxel, Cisplatin, and Fluorouracil; Docetaxel and Cisplatin; and Epirubicin, Cisplatin, and Fluorouracil As Systemic Treatment for Advanced Gastric Carcinoma: A Randomized Phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007; 25: 3217-3223.
3. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005; 23: 5660-5667.
4. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer Chemother Pharmacol 2010; 66: 31-36.

# Docetaxel – Capecitabine

## Indications:

- For metastatic or locally advanced gastric cancer (for both perioperative and non-surgical)

## Schedule

- Docetaxel 20 mg/m$^2$ IV on day 1.
- Capecitabine 625- 825 mg/m$^2$; PO bid on days 1-5
- Weekly for 5 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Czito BG, Kelsey CR, Hurwitz HI, et al. A Phase I study of capecitabine, carboplatin, and paclitaxel with external beam radiation therapy for esophageal carcinoma. Int J Radiat Oncol Biol Phys 2007; 67: 1002-1007.
3. Spigel DR, Greco FA, Meluch AA, et al. Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine, with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction. J Clin Oncol 2010; 28: 2213-2219.

# Carboplatin- Paclitaxel

## Indications:

- For metastatic or locally advanced gastric cancer (non-surgical)
  - Carboplatin AUC 2 IV on day 1
  - Paclitaxel, 200 mg/ $m^2$ IV day 1
  - Weekly for 5 weeks.

**OR**

- Carboplatin (AUC) 5 on day 1
- Paclitaxel, 200 mg/ $m^2$ IV day 1
- Repeat every 21 days.

## References:

1. National Comprehensive Cancer Network 2012.
2. Gadgeel SM, Shields AF, Helibrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Ann J Clin Oncol 2003; 26: 37-41.

# EOX (Epirubicin- Oxaliplatin-Capecitabine)

## Indications:

- For metastatic or locally advanced gastric cancer

## EOX Schedule:

- Epirubicin 50 mg/$m^2$ I.V. on day 1
- Oxaliplatin 130 mg/$m^2$ I.V. on day 1
- Capecitabine 625 mg/$m^2$ P.O. b.i.d.
- Repeat cycle every 21 days

## References:

1. Sumpter K. Br J Cancer 2005; 92: 1976-1983.

Chapter 1

# PANCREATIC CANCER

## Gemcitabine

## Indications:

- Metastatic or locally advanced pancreatic cancer.
- For post-operative adjuvant treatment of pancreatic cancer.

## Gemcitabine schedule

- Gemcitabine 1000 mg/m$^2$ IV over 30 mins; weekly.
- Repetition: weekly, 7 *(because of heamatotoxicity, frequently a pause is made on day 22); the day 1, 8, 15 repetition on day 29.
- Number of cycles: 6 (with cycle 1 over 7 weeks).
- Treat until disease progression.

## References:


1. National Comprehensive Cancer Network 2012.
2. Berlin JD et al. Phase III study of gemicitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group trial E2297. J. Clin. Oncol. 20 (2002): 3270-3275.
3. Bernhard J et al. Clinical benefit ana quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial-SAKK 44/00-CECOG/PAN. 1.3.001. J. Clin. Oncol. 26 (2008): 3695-3701.
4. Burris HA 3rd et al. Improvements in survival and clinical benefit with gemcitabine trial. J. Clin. Oncol. 15 (1997): 2403-2413.

# GEMOX Protocol (Gemcitabine + Oxaliplatin)

## Indications:

- Metastatic or locally advanced pancreatic cancer.

## GEMOX Schedule:

- Gemcitabine 1000 mg/m$^2$ IV (100 min inf), day 1
- Oxaliplatin 100 mg/m$^2$ IV (2 h inf), day 2
- To be repeated every 2 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Demols A et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br. J. Cancer 94 (2006): 481-485.
3. Lee KH et al. Gemitabine and oxaliplatin combination as first-line treatment for advanced pancreatic cancer: a multicenter phase II study. Cancer Chemother. Pharmacol. 64 (2009): 317-325.
4. Louvet C et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J. Clin. Oncol. 23 (2005): 3509-3516.

# 5 – FU + Folinic acid

## Indications:

- Metastatic or locally advanced pancreatic cancer
- For post-operative adjuvant treatment of pancreatic cancer.

## Schedule

- 5 – FU 425 mg/m² i.v b. d1-5 after
- Folinic acid 20 mg/m² i.v b. d1-5
- To be repeated every 4 weeks (6 cycles adjuvant)

## Oxaliplatin + Leucovorin + 5-FU protocol

## Indications:

- For metastatic pancreatic cancer
- Repeat every 43 days until disease progression.

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 8, 22 | Oxaliplatin | 85 | 5% Glucose | 500 | 2 hr | I.V. |
| 1, 8, 15, 22 | Leucovorin | 200 | 0.9% NaCl | 250 | 2 hr | I.V. |
| 1, 8, 15, 22 | 5-Fluorouracil | 2000 | 0.9% NaCl | 1000 | 24 hr | I.V. |
| * Leucovorin as a modulator of 5-FU should always be administered before 5-FU. | | | | | | |

## References:

1. National Comprehensive Cancer Network 2012.
2. Pelzer U. et al., Onkologie 32:99ff, 2009.

# Capecitabine

Capecitabine 1000 mg/m² twice daily; day 1-14 every 21 days for 3 weeks

## References:

1. National Comprehensive Cancer Network 2012.

# Gemcitabine + Capecitabine

## Indications:

- For metastatic pancreatic cancer

## Gemcitabine + Capecitabine schedule:

- Gemcitabine 1000 mg/$m^2$ I.V. (30 min inf) day 1+8
- Capecitabine 650 mg/$m^2$ b.i.d. P.O. days 1-14
- To be repeated every 3 weeks.
- OR
- Gemcitabine 1000 mg/$m^2$ I.V. (30 min inf) days 1, 8, and 15
- Capecitabine 830 mg/$m^2$ b.id. P.O. days 1-21
- To be repeated evry 4 weeks (until disease progression or intolerable toxicity).

## References:

1. Hermann R et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J. Oncol. 25 (2007): 2212-2217.
2. Cunningham D et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J. Clin. Oncol. 27 (2009): 5513-5518.

# GYNAECOLOGICAL CANCER

# Cervical Cancer

## Cis-RT (Chemoradiation: concomitant cisplatin with radical radiotherapy)

## Indications:

- Locally advanced stage IB2 to IVA cervical cancer.

| **Cis – RT schedule** | | **● = i.v.** |
|---|---|---|
| Day | 1 | 1- week cycle for 4-5 courses |
| Cisplatin, 40 mg/m² IV weekly (maximal dose 70 mg per week) with external beam RT, Followed by intracavity brachytherapy. | | |

- **Cisplatin is given 4 hours before radiation therapy on weeks 1-6.**

## References:

1. National Comprehensive Cancer Network 2012.

# Cisplatin + Vinorelbine

## Indications:

- For metastatic pancreatic cancer

## Cisplatin + Vinorelbine schedule:

- Cisplatin 80 mg/m$^2$ I.V. on day 1
- Vinorelbine 25 mg/m$^2$ I.V. on days 1 and 8.
- Repeat cycle every 21 days

## References:

1. Morris M et al. Phase II study of cisplatin and vinorelbine in squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J. Clin. Oncol. 22 (2004): 3340-3344.
2. Monk BJ et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistant cervical carcinoma: a Gynecologic Oncology Group study. J. Clin. Oncol. 27 (2009): 4649-4655.
3. Pignata S. J Clin Oncol 1999; 17: 756-760.

# Paclitaxel – Carboplatin Protocol

## Indications:

- Locally advanced stage cervical cancer.

## Paclitaxel – Carboplatin Schedule:

- Paclitaxel 175 mg/$m^2$ IV over 3 hours, day 1
- Carboplatin AUC of 5, IV on day 1
- Repeat cycle every 21 days.

## References:

1. Sit AS. Cancer Invest 2004; 22: 368-373.

# ENDOMETRIAL CANCER

## Paclitaxel – Carboplatin Protocol

### Indications:

- Locally advanced stage endometrial cancer.
- Adjuvant treated and metastatic disease.

### Paclitaxel – Carboplatin Schedule:

- Paclitaxel 175 mg/m$^2$ IV over 3 hours, day 1
- Carboplatin AUC of 5-7, IV on day 1
- Repeat cycle every 28 days.

### References:

1. Hoskins PJ, et al. Paclitaxel and carboplatin alone or with radiation in advanced or recurrent endometrial cancer: a phase II study. J Clin Oncol 2001; 19: 4048-4053.

# Cisplatin – doxorubicin

## Indications:

- Locally advanced or metastatic endometrial cancer

| **Cisplatin – doxorubicin schedule** | | **● = i.v.** |
|---|---|---|
| Day | 1 | 3- week cycle for 6 courses, depending on response |
| Doxorubicin, 50 mg/m² i.v. | ● | |
| Cisplatin, 50-60 mg/m² i.v. | ● | |

## References:


1. Aapro MS et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive resilts of a randomized study (55872) by the EORTC Gynaecological Cancer Group. Ann. Oncol. 14 (2003): 441-448.
2. Randall ME et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J. Clin. Oncol. 24 (2006): 36-44.


## Doxorubicin* + Paclitaxel

- Doxorubicin: 50 mg/m$^2$ IV on day 1.
- Paclitaxel: 150 mg /m$^2$ IV on day 1
- Repeat cycle every 21 days.

## References:


1. Fiorica JV. Update on the treatment of cervical and uterine carcinoma: focus on topotecan. Oncologist 2002; 7 (Suppl 5): 36-45.

# ENDOMETRIAL/MIXED MULLERIAN TUMORS

## CDCP (carboplatin – doxorubicin / carboplatin – paclitaxel)

## Indications:

- Locally advanced or metastatic endometrial cancer

| CDCP schedule | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle for 4 courses |
| Carboplatin (AUC 5) i.v. infusion* | ● | |
| Doxorubicin, 50 mg/m², bolus | | |

**FOLLOWRD BY**

| Day | 1 | 3- week cycle for 4 courses |
|---|---|---|
| Carboplatin (AUC 5) i.v. infusion* | ● | |
| Paclitaxel, 175 mg/m² transfused over 3 hours | ● | |

*Carboplatin dose should be calculated by the formula :

Dose in mg = 5× [EDTA clearance + 25], where EDTA clearance is in ml/ minute

Chapter 1

# OVARIAN CANCER

## CAP (Cisplatin – doxorubicin – cyclophoamide)

## Indications:

- Metastatic or locally advanced ovarian cancer

| **CAP schedule** | | **● = i.v.** |
|---|---|---|
| Day | 1 | 3- week cycle for 6 courses |
| Cisplatin, 50 mg/m² i.v. | ● | |
| Doxorubicin, 50 mg/m² | ● | |
| Cyclophoamide, 500 mg/m² i.v. | ● | |

## Paclitaxel- Carboplatin

## Indications:

- Epithelial ovarian cancer / Fallopian tube cancer / Primary peritoneal cancer

## Paclitaxel- Carboplatin Schedule:

- Paclitaxel, 175 mg/ m² I.V over 3 hours
- Carboplatin, AUC 5.0- 7.5
- Paclitaxel is administered before carboplatin.
- Paclitaxel-accompanying medication: dexamethasone 20 mg I.V. 30 mins before paclitaxel, or dexamethasone 20 mg oral administration 6 hrs and 12 hrs before paclitaxel. Additional premedication with 50 mg ranitidine and 30 mg Diphenhydramine is recommended.
- Repeat every 21 days for 6 cycles.

## References:


1. National Comprehensive Cancer Network 2012.
2. Vasey P.A et al., J Natl Cancer Inst 96: 1682ff, 2004.
3. Ozols RE. Combination regimens of paclitaxel and the platinum drugs as first-line regimens for ovarian cancer. Semin Oncol 1995; 22 (Suppl 15): 1-6.
4. Bolis G et al. Paclitaxel/carboplatin versus topotecan/paclitaxel/carboplatin in patients with FIGO suboptimally resected stage III-IV epithelial ovarian cancer a multicenter, randomized study. Eur. J. Cancer 46 (2010): 2905-2912.
5. Hoskins P et al. Advanced ovarian cancer: phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel vs carboplatin-paclitaxel. J. Nalt. Cancer Inst. 102 (2010): 1547-1556.

## Cisplatin- Paclitaxel

## Indications:

- Epithelial ovarian cancer / Fallopian tube cancer / Primary peritoneal cancer

## Schedule:

Paclitaxel, 135 mg/ m² I.V (3 hr or 24 hr inf), day 1
Cisplatin, 75 mg/ m² I.V (1 mg/min), on day 1 or 2
Paclitaxel must be administered first followed by cisplatin.
Repeat every 21 days.

## References:

1. National Comprehensive Cancer Network 2012.
2. McGuire WP et al. Cyclopgosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N. Engl. J. Med. 334 (1996): 1-6.
3. Spriggs DR et al. Phase III randomized trial of intravenous cisplatin plus a 24- or 96- hour infusion of paclitaxel in epithelial ovarian cancer: a Gynecologic Oncology Group Study. J. Clin. Oncol. 25 (2007): 4466-4471.

# Paclitaxel

## Indications:

- Epithelial ovarian cancer / Fallopian tube cancer / Primary peritoneal cancer

## Paclitaxel Schedule:

- Paclitaxel, 175 mg/ m² I.V (over 3 hours or 24 hours) on day 1
- Repeat every 21 days.

## References:

1. Omura GA et al. Phase III trial of paclitaxel at two dose levels, the higher dose accompanied by filgrastim at dose levels in platinum-pretreated epithelial ovarian cancer: an intergroup study. J. Clin. Oncol. 21 (2003): 2843-2848.
2. Ten Bokkel Huinink W et al. Long-term survival in a phase III, randomized study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. Ann. Oncol. 15 (2004): 100-103.

# Carboplatin

## Indications:

- Metastatic or locally advanced ovarian cancer where carboplatin – paclitaxel is not appropriate (if platinum sensitive)
- Epithelial ovarian cancer / Fallopian tube cancer / Primary peritoneal cancer
- Repeat every 22 days for 6 cycles.

**Carboplatin schedule** ● = i.v.

| Day | 1 | 3 or 4 week cycle for 6 cycles |
|---|---|---|
| Carboplatin (AUC) 5-6 i.v. infused over 1 hr | ● | |

*Carboplatin dose should be calculated by the formula :

Dose in mg = 5× [EDTA clearance + 25], where EDTA clearance is in ml/minute

Formula becomes inaccurate for EDTA clearance below 40 ml/minute

- Calculation of carboplatin dose:

According to AUC methods (Clavert): 5*(GFR +25) mg

According to Cockcroft and Gault: 6*(GFR + 25) mg

## References:

1. National Comprehensive Cancer Network 2012.
2. Reed NS et al. A randomized comparison of treosulfan and carboplatin in patients with ovarian caner: A study by the Scottish Gynaecological Cancer Trials Group (SGCTG). Eur. J. Cancer 42 (2006): 179-185.

# Docetaxel– Carboplatin

## Indications:

- Metastatic or locally advanced ovarian cancer
- Epithelial ovarian cancer / Fallopian tube cancer / Primary peritoneal cancer

| **Docetaxel– Carboplatin schedule** | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle for 6-8 courses |
| Docetaxel, 75 mg/m² i.v. 1h infusion | ● | |
| **FOLLOWRD BY** | | |
| Carboplatin (AUC 5) i.v. infused over 1 hour* | ● | |

*Carboplatin dose should be calculated by the formula:

Dose in mg = 5×[ EDTA clearance + 25 ] , where EDTA clearance is in ml/ minute

Formula becomes inaccurate for EDTA clearance below 40 ml/minute

- Calculation of carboplatin dose:

According to AUC methods (Clavert): 5*(GFR +25) mg

According to Cockcroft and Gault: 6*(GFR + 25) mg

# Carboplatin / Cyclophosphamide Protocol

## Indications:

- Metastatic or locally advanced ovarian cancer
- Epithelial ovarian cancer / Fallopian tube cancer / Primary peritoneal cancer

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Carboplatin | 300 | 5% Glucose | 500 | 1 hr | I.V. |
| 1 | Cyclophosphamide | 600 | 0.9% NaCl | 500 | 1 hr | I.V. |

| Day | Carboplatin + Cyclophosphamide Day 1 | Carboplatin + Cyclophosphamide Day 29 |
|---|---|---|
| | 1----------29---------- | |
| Cycle | 1 | 2 |

- Repeat every 29 days for 6 cycles.
- Mesna: 20% of the dose of cyclophosphamide (if total dose >1000 mg) I.V. or orally 0 hr, 4 hr, 8 hr after cyclophosphamide administration. Adequate dieresis.

## References:

1. Swenerton K. et al., J Clin Oncol 10: 718 ff, 1992.
2. National Comprehensive Cancer Network 2012.

# Gemcitabine – Carboplatin Protocol

## Indications:

- Used in treatment of epithelial ovarian cancer/ fallopian tube cancer/ primary peritoneal cancer.
- Used in advanced metastatic ovarian carcinoma.

## Gemcitabine-carboplatin schedule:

- Gemcitabine 1000 mg/m$^2$ IV (30 min inf), day 1and 8
- Carboplatin AUC 4-5 IV, day 1
- To be repeated evry 3 weeks (up to a max of 10 cycles).

## References:

1. National Comprehensive Cancer Network 2012.
2. Pfisterer J et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG, J. Clin. Oncol. 24 (2006): 4699-4707.
3. Sufliarsky J et al. Gemcitabine and carboplatin treatment in patients with replasing ovarian cancer. Neoplasma 56 (2009): 291-297.

# Hormonal therapy

- **Letrozole**
- **Leuprolide acetate**
- **Megestrol acetate**
- **Tamoxifen**

# OVARIAN GERM CELL TUMOR

**BEP (Bleomycin – Etoposide – Cisplatin)**

## Indications:

- Stage I – IV malignant ovarian germ cell tumors

**BEP schedule** **● = i.v.**

| Day | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 3- week cycle for 3-4 courses |
|---|---|---|---|---|---|---|---|---|
| Bleomycin, 30 IU i.v. | ● | | | | ● | ● | | No bleomycin for course 3 |
| And subsequent depending on histology and pathology | | | | | | | | |
| Etoposide, 100 mg/m² i.v. | ● | ● | ● | ● | ● | | | |
| Cisplatin, 20 mg/m² i.v. | ● | ● | ● | ● | ● | | | |

# TROPHOBLASTIC TUMORS (LOW RISK)

**Methotrexate**

## Indications:

- Low – risk gestational trophoblastic tumors

**Methotrexate schedule** ■ = i.m. o = p.o.

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Methotrexate, 50mg i.m. at1200 hours | ■ | | ■ | | ■ | | | |
| Folinic acid, 7.5 mg p.o at 1800 hours | | o | | o | | o | | o |

Repeat after 6 drug- free days

# TROPHOBLASTIC TUMORS (MEDIUM AND HIGH RISK)

**EMACO (Etoposide – Methotrexate – Actinomycin D-cyclophpsphamide – Vincristine)**

## Indications:

- Medium – and high - risk gestational Trophoblastic tumors

| **EMACO schedule** | | | | | ● = i.v. ■ = i.m. o = p.o. |
|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 8 | Give EMA and CO |
| Alternate weeks | | | | | |
| Etoposide, 100 mg/m² i.v. | ● | ● | | | |
| Actinomycin D, 0.5 mg i.v. | ● | ● | | | |
| Methotrexate, 300 mg/m²i.v.infusion over 12 days | ● | | | | |
| Folinic acid, 15 mg p.o/i.m.b.d., doses | | o/■ | o/■ | | |
| Starting 24 hours after Methotrexate | | | | | |
| Cyclophosphamide, 600 mg/m² i.v. over 30 minute's | | | | ● | |
| Vincristine, 0.8 mg/m² i.v. (maximum 2 mg) | | | | ● | |

# HEAD AND NECK CANCER

**Cisplatin, 5 – fluorouracil**

## Indications:

- Palliative chemotherapy for recurrent or metastatic squamous cell head and neck cancer
- Neoadjuvant chemotherapy for squamous cell head and neck cancer as primary systemic therapy combined with radiotherapy.
- Adjuvant chemotherapy for nasopharyngeal cancer combined with radiotherapy.
- Recurrent / unresectable / or metastatic (incurable) nasopharynx cancers.

**Cisplatin – 5 – FU schedule** ● = i.v.

| Day | 1 | 2 | 3 | 4 | 5 | 3- week cycle |
|---|---|---|---|---|---|---|
| Cisplatin, 100 mg/m² i.v.infusion | ● | | | | | |
| 5-Fu, 1000 mg/m², 24-hour infusion | ● | ● | ● | ● | ● | |

* For nasopharyngeal cancer, cisplatin 80 mg/m²

| D | Drug | Do, mg/m² | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Cisplatin | 100 | 0.9% NaCl | 1000 | 4 hrs | I.V. |
| 1-5 | 5-Fluorouracil | 1000 | 0.9% NaCl | 1000 | 24 hrs | I.V. |
| Repeat every 29 days for 6 cycles<br>Cisplatin (only if GFR ≥60ml/min):<br>Accompanying medication: Premedication: 250 ml mannite 20% or 40 mg furosemide I.V.<br>Postmedication: 3* 1000 ml 0.9% NaCl I.V. and electrolyte balance. | | | | | | |

## References:


1. National Comprehensive Cancer Network 2012.
2. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advancedhead and neck cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005; 23: 3562-3567.
3. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck: A Southwest Oncology Group Study. J Clin Oncol 1992; 10: 1245-1251.
4. Kish JA et al. Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidemoid cancer of the head and neck. Cancer 53 (1984): 1819-1824.

# Paclitaxel

## Indications:

- Advanced head and neck cancer

## Paclitaxel Schedule:

- Paclitaxel, 250 mg/ $m^2$ I.V day 1 over 24 hours
- Repeat every 21 days.

OR

- Paclitaxel 135-175 mg/$m^2$ IV over 3 hours on day 1
- Repeat cycle every 21 days.
- Granulocyte colony- stimulating factor is used to prevent neutropenia.

## References:

1. National Comprehensive Cancer Network 2012.
2. Forastiere AA. Current and future trials of taxol (paclitaxel) in head and neck cancer. Ann Oncol 1994;5 (Suppl 6): 51-54.

# Paclitaxel/ carboplatin

Paclitaxel, 175 mg/ m² I.V over 3 hours on day 1
Carboplatin, AUC of 6 I.V day 1
G-CSF, 5 mcg/ kg/ day s.q. days 2-12
* Cycles repeated every 21 days.

## References:

1. National Comprehensive Cancer Network 2012.
2. Fountazilas G, et al. Paclitaxel and carboplatin in recurrent or metastatic head and neck cancer: a phase II study. Semin Oncol 1997; 24 (Suppl 15): 65-67.

# Paclitaxel/ Cisplatin

Paclitaxel, 175 mg/ m² I.V over 3 hours day 1
Cisplatin, 75 mg/ m² I.V day 2
G-CSF, 5 mcg/ kg/ day s.q. days 4-10
Cycles repeated every 21 days.

## References:

1. National Comprehensive Cancer Network 2012.
2. Hitt R, et al. A phase I/II study of paclitaxel plus cisplatin as first-line therapy for head and neck cancer. Semin Oncol 1995; 22 (Suppl 15): 50-54.

# Docetaxel /Cisplatin /5-Fluorouracil

## Indications:

- Induction/ sequential chemotherapy for squamous cell cancers.

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Docetaxel | 75 | 0.9% NaCl | 250 | 1 hr | I.V. |
| 1 | Cisplatin | 75 or 100 | 0.9% NaCl | 500-1000 | 2 hrs | I.V. |
| 1-5 | 5-Fluorouracil | 750 | 0.9% NaCl | 1000 | 24 hrs | I.V. |
| Repeat every 21 days. (3 cycles for induction therapy, 4 cycles for unresectable disease). | | | | | | |

- Docetaxel should be dissolved at 0.32-0.74 mg/ml
- Accompaning medication: Dexamethasone 8 mg orally 2*daily for 3 days starting one day before Docetaxel administration.
- Cisplatin (only if GFR ≥60ml/min):
- Accompanying medication: Premedication: 250 ml mannite 20% or 40 mg furosemide I.V.

Postmedication: 3* 1000 ml 0.9% NaCl I.V. and electrolyte balance.

## References:

1. National Comprehensive Cancer Network 2012.
2. Posner MR et al; TAX 324 study group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N. Engl. J. Med. 357 (2007): 1705-1715.
3. Vermorken JB et al. EROTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N. Engl. J. Med. 357 (2007): 1695-1704.

# Capecitabine

## Indications:

- Advanced head and neck cancer

## Schedule

Capecitabine 1250 mg/m² BID for 14 days (one week rest)

# Gemcitabine Monotherapy

## Indications:

- Recurrent / unresectable / or metastatic (incurable) nasopharynx cancers.

| D | Drug | Do, mg/m² | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1, 8, 15 | Gemcitabine | 1000 | 0.9% NaCl | 250 | 30mins | I.V. |
| Repeat every 29 days for 6 cycles. | | | | | | |

## References:

1. National Comprehensive Cancer Network 2012.
2. Catimel G. et al., Ann Oncol 5: 543ff, 1994.

# Docetaxel Monotherapy protocol

## Indications:

- Recurrent / unresectable / or metastatic (incurable) nasopharynx (head and neck) cancers.

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Docetaxel | 60-100 | 0.9% NaCl | 250 | 1 hr | I.V. |
| Repeat every 22 days for 6 cycles. | | | | | | |

- Docetaxel should be dissolved at 0.32-0.74 mg/ml
- Accompaning medication: Dexamethasone 8 mg orally 2*daily for 3 days starting one day before Docetaxel administration.

## References:

1. National Comprehensive Cancer Network 2012.
2. Catimel G. et al., Ann Oncol 5: 533ff, 1994.
3. Dreyfuss A, et al. Taxotere for advanced, inoperable squamous cell carcinoma of the head and neck (SCCHN). Proc Am Soc Clin Oncol 1995; 14: 875a.

# LUNG CANCER

# Mesothelioma

**MVP (Mitomycin C – Vinblastine – Cisplatin)**

## Indications:

- Palliative chemotherapy of Mesothelioma

| **MVP schedule** | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle for 4 courses |
| Mitomycin C, 8 mg/m² i.v. | ● | Mytomycin C in courses 1,2 and only |
| Vinblastine, 6 mg/m² i.v. | ● | |
| (Maximum total 10 mg) | | |
| Cisplatin, 50 mg/m² i.v. infusion | ● | |

## References:

1. National Comprehensive Cancer Network 2012.
2. Vogelzang NJ et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J. Clin. Oncol. 21 (2003): 2636-2644.

Chapter 1

# Gemcitabine – Cisplatin

## Indications:

- First-line combination chemotherapy for malignant pleural mesothelioma.

Gemcitabine/ Cisplatin schedule:

- Gemcitabine 1000-1250 mg/m$^2$ day 1, 8, and 15
- Cisplatin 80-100 mg/m$^2$ day 1
- Administer in 3-4 week cycles.

## References:


1. National Comprehensive Cancer Network 2012.
2. Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine foe malignant mesothelioma. Br J Cancer 2002; 87: 491-496.
3. Van Haarst JM, Baas J, Manegold CH, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer 2002; 86: 342-345.

# Vinorelbine Monotherapy *

## Indications:

- First-line monotherapy for malignant pleural mesothelioma.
- Second-line chemotherapy for malignant pleural mesothelioma

Vinorelbine schedule:

- Vinorelbine 25-30 mg/m$^2$ I.V. weekly

## References:

1. National Comprehensive Cancer Network 2012.
2. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomized trial. Lancet 2008; 371: 1685-1694.

Chapter 1

# NON – SMALL CELL LUNG CANCER

## Carboplatin – paclitaxel

## Indications:

- Palliative treatment of advanced NSCLC
- Neoadjuvant chemotherapy prior to planned radical treatment of primary NSCLC

| **Carboplatin – paclitaxel schedule** | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle |
| Paclitaxel, 175-200 (up to 225) mg/m² i.v. over 3 hours | ● | |
| Carboplatin (AUC 6) i.v. infusion* | ● | |

- Important to administer paclitaxel first followed by carboplatin.

*Carboplatin dose should be calculated by the formula :

Dose in mg = 6× [EDTA clearance + 25], where EDTA clearance is in ml/ minute

## References:


1. National Comprehensive Cancer Network 2012.
2. Strauss GM, Herndon III JE, MAddus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in satge IB non-small cell lung cancer; CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008; 26: 5043-5051.
3. Belani CP et al. Randomized, phase III study of weekly paclitaxel in combination withcarboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J. Clin. Oncol. 26 (2008): 468-473.
4. Belani CP et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann. Oncol. 16 (2005): 1069-1075.
5. Kubota K et al; Japan Multi-National Trial Organization Collaborates. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomized, open-label, phase III study. Lancet Oncol. 9 (2008): 1135-1142.

# Paclitaxel/ Cisplatin

## Indications:

- Neoadjuvant chemotherapy prior to planned radical treatment of NSCLC

## Paclitaxel + Cisplatin schedule:

- Paclitaxel 135 mg/ m² i.v. over 3 hours or 24 hours inf, day 1
- Cisplatin 75 mg/ m² i.v. (1 hr inf), on day 2 (after paclitaxel)
- Repeat every 3 weeks.
- Important to administer paclitaxel first followed by cisplatin
- Premedicate before paclitaxel.

## References:

1. Schiller JH et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N. Engl. J. Med. 346 (2002): 92-98.

# Gemcitabine

## Indication:

- Palliation of advanced NSCLC
- Systemic therapy for advanced or metastatic disease in NSCLC

## Gemcitabine schedule:

- Gemcitabine 1000-1250 mg/m$^2$ I.V. (30 min inf), day 1 and 8
- To be repeated every 3 weeks (max 6 cycles).

## References:

1. National Comprehensive Cancer Network 2012.
2. Coskun U et al. Single agent gemcitabine in the second-line treatment of advanced non-small cell lung cancer after treatment with taxane + platinum regimens. Med. Oncol. 25 (2008): 133-136.
3. Gridelli C et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicentre Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J. Natl. Cancer Inst. 95 (2003): 362-372.
4. Lara PN et al. Gemcitabine in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: a phase II California Cancer Consortium trial. Clin. Lung Cancer 6 (2004): 102-107.

# Gemcitabine – carboplatin or Cisplatin

## Indications:

- Palliative treatment of advanced NSCLC
- Neoadjuvant chemotherapy prior to planned radical treatment of primary NSCLC
- Systemic therapy for advanced or metastatic disease in NSCLC

## Gemcitabine – Carboplatin or cisplatin schedule

- Gemcitabine 1000-1250 mg/m$^2$ I.V. (30-60 min inf), day 1 and 8
- Carboplatin AUC= 5 or 5.5 I.V. (15-60 min inf), day 1
- To be repeated every 3 weeks.

**OR**

- Gemcitabine 1000 mg/m$^2$ I.V. (30-60 min inf), day 1, 8 and 15
- Cisplatin 100 mg/m$^2$ IV (30-120 min inf), day 1
- To be repeated every 4 weeks.

Carboplatin dose should be calculated by the formula:
Dose in mg = 5× [EDTA clearance + 25], where EDTA clearance is in ml/minute

## References:


1. National Comprehensive Cancer Network 2012.
2. Sandler AB et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J. Clin. Oncol. 18 (2000): 122-130.
3. Masters GA et al. A randomized phase II trial using two different treatment schedules of gemcitabine and carboplatin in patients with advanced non-small-cell lung cancer. J. Thorac. Oncol. 1 (2006): 19-24.
4. Sederholm C et al. Phase III trail of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: the Swedish Lung Cancer Study Group. J. Clin. Oncol. 23 (2005): 8380-8388.
5. Treat JA et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. Ann. Oncol. 21 (2010): 540-547.

# MVP (Mitomycin C – Vinblastine- Cisplatin)

## Indications:

- Palliative treatment of advanced NSCLC
- Neoadjuvant chemotherapy prior to planned radical treatment of primary NSCLC

| **MVP schedule** | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle for 3 courses |
| Mitomycin C, 8 mg/m² i.v | ● | Mitomycin C in courses 1 and 2 only |
| Vinblastin, 6mg/m² i.v (maximum total 10mg) | ● | |
| Cisplatin, 50 mg/m² i.v infusion | ● | |

## Docetaxel

## Indications:

- First line and relapsed locally advanced and metastatic non-small cell lung cancer
- Systemic therapy for advanced or metastatic disease in NSCLC

| **Docetaxel schedule** | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle |
| Docetaxel, 60-75 mg/m² i.v infusion | ● | |

OR

| |
|---|
| Docetaxel: 33.3-36 mg/m$^2$ IV weekly for 6 weeks |
| Repeat cycle every 8 weeks after 2-week rest |

## References:


1. National Comprehensive Cancer Network 2012.
2. Hanna N et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J. Clin. Oncol. 22 (2004): 1589-1597.
3. Segawa Y et al. A randomized phase II stud y of a combination of docetaxel and S-1 versus docetaxel monotherapy in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy: results of Okayama Lung Cancer Study Group (OLCSG) Trial 0503. J. Thorac. Oncol. 5 (2010): 1430-1434.
4. Camps C et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. Ann. Oncol. 17 (2006): 467-472.

# Docetaxel – Cisplatin/ Carboplatin

## Indications:

- First line NSCLC
- Systemic therapy for advanced or metastatic disease in NSCLC

| **Docetaxel – Cisplatin schedule** | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle |
| Docetaxel, 75 mg/m² i.v infusion 1h | ● | followed immediately by |
| Cisplatin 75 mg/m² i.v infusion 1h | ● | |
| OR | | |
| Carboplatin AUC6 i.v infusion 1-2h | ● | |

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Docetaxel | 75 | 0.9% NaCl | 250 | 1 hr | I.V. |
| 1 | Cisplatin | 75 | 0.9% NaCl | 1000 | 1 hr | I.V. |
| Repeat every 22 days for 6 cycles. | | | | | | |

- Docetaxel should be dissolved at 0.32-0.74 mg/ml
- Accompanying medication: Dexamethasone 8 mg orally 2* daily for 3 days starting one day before Docetaxel administration.
- Cisplatin (only if GFR ≥60ml/min):
- Accompanying medication: Premedication: 250 ml mannite 20% or 40 mg furosemide I.V.

Postmedication: 2 - 3* 1000 ml 0.9% NaCl I.V. and electrolyte balance.

# SMALL CELL LUNG CANCER

## Cisplatin + Etoposide Protocol

### Indications:

- First-line treatment for small cell lung caner

### Cisplatin + Etopside Schedule:

- Cisplatin 80 mg/$m^2$ IV (1 hr inf), day 1
- Etoposide 80 or 100 mg/$m^2$ IV (1 hr inf), days 1-3
- To be repeated every 3 weeks for 6 cycles.

### References:

1. National Comprehensive Cancer Network 2012.
2. Niell HB et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. J. Oncol. 23 (2005): 3752-3759.
3. Zatloukal P et al. A multicenter international randomized phase III studies comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease. Ann. Oncol. 21 (2010): 1810-1816.

# ACE (Doxorubicin – Cyclophosphamide – Etoposide)

## Indications:

- Limited – stage SCLC
- Extensive – stage SCLC

**ACE schedule** ● = i.v. o = p.o.

| Day | 1 | 2 | 3 | 3- week cycle for 4-6 courses |
|---|---|---|---|---|
| Cyclophosphamide, 600 mg/m² i.v | ● | | | |
| Doxorubicin, 40 mg/m² i.v | ● | | | |
| Etoposide, 100 mg/m² i.v infusion | ● | ●/o* | ●/o* | |

* Alternatively , etoposide, 100 mg/m² b.d.p.o., nay be given on days 2 and 3

Cyclophosphamide, 1000 mg/m², and etoposide, 120 mg/m², may be used as an alternative intravenous regimen but cause a much greater degree of myelosuppression

## Carboplatin – etoposide

## Indications:

- Limited – stage SCLC
- Extensive – stage SCLC

**Carboplatin – etoposide schedule** ● = i.v. o = p.o.

| Day | 1 | 2 | 3 | 3- week cycle for 4-6 courses |
|---|---|---|---|---|
| Etoposide, 100mg/m² i.v. infusion | ● | ●/o* | ●/o* | |
| Carboplatin. (AUC 5) i.v. * * | ● | | | |

* Etoposide, 100 mg/m² b.d.p.o., May be substituted on days 2 and 3

* * Carboplatin dose should be calculated by the formula :

Dose in mg = 5×[ EDTA clearance + 25 ] , where EDTA clearance is in ml/minute

# Etoposide (oral)

## Indications:

- Palliative therapy in patients with SCLC not suitable for intravenous or combination therapy
- Salvage therapy in SCLC

| Etoposide (oral) schedule | | | | | | o = p.o. |
|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 3- week cycle |
| | | | | | | For 3-6 courses, |
| | | | | | | According to response |
| Etoposide, 50 mg* p.o.b.d. | o | o | o | o | o | |

*Dose escalate in courses 2 and 3 if well tolerated

# EVANS Protocol:

## Indications:

1.Extensive stages
2.Relapses > 2-3 months up to 6 months

## EVANS Schedule:

- CAV (Cyclophosphamide- Adrimaycin- Vincristine)
- Cisplatin/Etoposide

CAV (Cyclophosphamide- Adrimaycin- Vincristine)

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Doxorubicin | 50 | 0.9% NaCl | 500 | 1 hr | IV |
| 1 | Cyclophosphamide | 1000 | 0.9% NaCl | 1000 | 2 hr | IV |
| 1 | Vincristine | 1.4 (*) | 0.9% NaCl | 100 | 10 ‘ | IV |

| Day | Doxorubicin/Cyclophoshamide/Vincristine Day 1 | | Cisplatin/Etoposide Day 22,23,24 | |
|---|---|---|---|---|
| | 1 | 22-24 | 43- | |
| Cycle | 1 | | 2 | 3 |
| Repetition: Day 22 (alternating)<br>Number of cycles: 6 (3* CAV and 3* Cisplatin/Etoposide alternatingly) | | | | |

**Cisplatin/Etoposide**
**Notes:**

- Cisplatin (only if GFR ≥ 60 ml/min), accompanying medication: premedication: 250 ml Mannite 20% or 40 mg Furosemide IV; postmedication: 1000 ml 0.9% NaCl IV and electrolyte balance.
- Cisplatin may be substituted by Carboplatin.
- Caution: Cardiac toxicity of Doxorubicin at cumulative dose ≥500 mg/m$^2$.
- (*) Vincristine max. 2 mg total doses.
- Mesna 20 % of Cyclophosphamide dose IV or orally 0 hr, 4 hr, 8 hr after administration of Cyclophosphamide. Adequate diuresis.
- Etoposide should be dissolved in 1000 ml 0.9% NaCl if total dose is ≥ 200 mg.

## References:

1. National Comprehensive Cancer Network 2012.
2. Van Pawel J, Schiller JH, and Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999; 17 (2): 658-667.
3. Evans W.K. et al., Ann Int Med 107: 451ff, 1987.

# MALIGNANT MELANOMA

## Dacarbazine (DTIC)

## Indications:

- Systemic therapy for advanced or metastatic melanoma

**Dacarbazine (DTIC) schedule** ● = i.v.

| Day | 1 | 2 | 3 | 4 | 5 | 3- week cycle |
|---|---|---|---|---|---|---|
| Dacarbazine 850-1000 mg/m² i.v Short inf. | ● | | | | | |
| OR | | | | | | |
| Dacarbazine 250 mg/m² i.v Short inf. | ● | ● | ● | ● | ● | |
| OR | | | | | | |
| Dacarbazine 850 mg/m² i.v in 0.9% Saline 500ml over 1h | ● | | | | | |

## CVD Protocol (Cisplatin+ Vinblastine + Dacarbazine)

## Indications:

- Systemic therapy for advanced or metastatic melanoma

## CVD Schedule:

- Cisplatin 20 mg/m$^2$ IV (30 min inf), day 1-4
- Vinblastine 1.2 or 2 mg/m$^2$ IV, day 1-4
- Dacarbazine 800 mg/m$^2$ IV (1 hr inf), day 1
- To be repeated every 3 weeks.

## References:

1. Atkins MB et al. Phase II trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Easrtern Cooperative Oncology Group. Clin. Oncol. 26 (2008): 5748-5754.
2. Eton O et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J. Clin. Oncol. 20 (2002): 2045-2052.

Chapter 1

# Interferon alpha

## 1. Low-dose interferon alpha
## Indications:

- Systemic therapy for advanced or metastatic melanoma

## Interferon alpha Schedule:

- Interferon alpha 3 MU S.C. (3*weekly), for 18-24 months.
- To be repeated every 4 weeks.

## References:


1. Hauschild A et al. Prospective randomized multicenter adjuvant dermatologic cooperative oncology group trial of low-dose interferon alfa-2b with or without a modified high-dose interferon alfa-2b induction phase in patients with lymph node-negative melanoma. J. Clin. Oncol. 27 (2009): 3496-3502.
2. Hauschild A et al. Efficacy of low-dose interferon α2a 18 versus 60 months of treatment in patients with primary melanoma ≥ of 1.5 mm tu mor thikness: Results of a randomized phase III DeCOG trial. J. Clin. Oncol. 28 (2010): 841-846.


## 2. High -dose interferon alpha

## Indications:

- Systemic therapy for advanced or metastatic melanoma

## Interferon alpha Schedule:

- Interferon alpha 15-20 MU/$m^2$ I.V. (or I.M.) 5 d/wk, for 4 wks then 10 MU/$m^2$ S.C> 3* weekly, for 48 wks.

## References:


1. Kirkwood JM et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology trial EST 1684. J. Clin. Oncol. 14 (199): 7-17.
2. Pectasides D et al. Randomized phase III study of 1 month versus 1 year of adjuvant high-dose interferon alfa-2b in patients with resected high-risk melanoma. J. Clin. Oncol. 27 (2009): 939-944.

# PROSTATE CANCER

## 1. Chemotherapy Protocols

### a. Combination Regimens
### Mitoxantrone

### Indications:

- Palliative therapy in hormone – resistant prostate cancer

| Mitoxantrone schedule | | ● = i.v. |
|---|---|---|
| Day | 1 | 3- week cycle |
| Mitoxantrone, 12 mg/m² i.v infusion | ● | |

### Docetaxel / Prednisolone (or Prednisone) Protocol

### Indications:

- Metastatic prostate cancer
- To prolong survival in hormone-refractory metastatic prostate cancer
- In hormone refractory prostate cancer

### Docetaxel / Prednisolone (or Prednisone) schedule:

| D | Drug | Do | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Docetaxel | 75 mg/m$^2$ | 0.9% NaCl | 250 | 1 hr | I.V. |
| 1-* | Prednisolone | 5 mg | ------- | ------- | ------- | P.O. |
| Repeat every 22 days for 6 cycles. | | | | | | |

### Notes:

- Docetaxel should be dissolved at 0.32 – 0.74 mg/ml
- Accompanying medication: Dexamethasone 4 mg orally 12 hr, 6 hr, 1 hr before and 12 hrs, 24 hrs, 36 hrs after Docetaxel administration. If there are no hyperseneitivity reactions, Dexamethasone dose can be reduced to 2*4 mg orally on the day of Docetaxel administration.

## References:

1. Bethold DR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J. Clin. Oncol. 26 (2008): 242-245.
2. Ide H et al. Docetaxel in combination with prednisolone for hormone refractory prostate cancer. Jpn. J. Clin. Oncol. 40 (2010): 79-84.
3. Machiels J-P et al. Prospective randomized study comparing doctaxel, estramustine, and prednisone with docetaxel and prednisone in metastatic hormone-refractory prostate cancer. J. Clin. Oncol. 26 (2008): 5261-5268.
4. Mountzios I et al. Intermittent docetaxel chemotherapy in patients with castrate-resistant prostate cancer. Urology77 (2011): 682-687.

## b. Single-Agent Regimen

## Paclitaxel

## Indications:

- In hormone refractory prostate cancer

Paclitaxel, 135- 170 mg/ m² IV over 24 hours on day 1

- Repeat every 21 days.

## References:

1. Roth BJ, et al. Taxol in advanced, hormone-refractory carcinoma of the prostate. A phase II trial of the Eastern Cooperative Ocnology Group. Cancer 1993; 72: 2457-2260.
2. Ahmed S, et al. Feasibility of weekly 1 hr paclitaxel in hormone refractory prostate cancer (HRPC): a preliminary report of a phase II trial. Proc Ann Soc Clin Oncol 1998; 17: 325a.

# Docetaxel

## Indications:

- In hormone refractory prostate cancer

## Docetaxel schedule

Docetaxel 75 mg/$m^2$ I.V. on day 1

- Repeat cycle every 21 days.

OR

Docetaxel 20-40 mg/$m^2$ weekly for 3 weeks

- Repeat cycle every 4 weeks.

## References:

1. Petrylak DP. Docetaxel (Taxotere) in hormone-refractory prostate cancer. Semin Oncol 2000; 27 (Suppl 3): 24-29.

# 2. Hormonal Therapy

- Goserelin acetate 3.6 mg S.C on day 1 monthly
- OR
- Goserelin 10.8 mg S.C. on day 1, repeat cycle every 12 weeks (3 months).

- Bicalutamide 50 mg P.O. bid, in patients with refractory to other antiandrogen agenst, may start with a higher dose of 150 mg P.O. daily.
  OR
- Bicalutamide 50 mg or 80 mg (for combined androgen blockade) P.O. daily **OR** 150 mg (for monotherapy) P.O. daily.

## References:


1. Akaza H et al; Combined Androgen Blockade Thearpy of Prostate Cancer. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-trm follow-up of a phase 3, double-blind, randomized study for survival. Cancer 115 (2009): 3437-3445.
2. Iversen P et al; Scandinavian Prostate Cancer Group. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand. J. Urol. Nephrol. 40 (2006): 441-452.
3. Dijkman GA, et al. A randomized trial comparing the safety and efficacy of the Zoladex 10.8-mg depot, administered every 12 weeks, to that of the Zoladex 3.6-mg depot, administered every 4 weeks, in patients with advanced prostate cancer. The Dutch South East Cooperative Urological Group. Eur Urol 1995; 27: 43-46.
4. The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl Med 1984; 911: 1281-1286.
5. Sharif R, et al. Leuprolide acetate 22.5 mg 12-week depot formulation in the treatment of patients with advanced prostate cancer. Clin Ther 1996; 18: 647-657.
6. Schellhammer PF, et al. Clinical benefits of biclutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multi-center trial. Casodex Combination Study Group. Urology 1997; 50: 330-336.
7. McLeod DG, et al. The use of flutamide in hormone-refractory metastatic prostate cancer. Cancer 1993; 72: 3870-3873.
8. Janknegt RA, et al. Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. J Urol 1993; 149: 77-82.

# RENAL CELL CARCINOMA

## Interferon – α

- Interferon alpha 5-10 MU/$m^2$ S.C. or I.M., daily or 3*weekly
- Until tumor progression (max 1 year in responders)

## References:

1. Flanigan RC et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N. Engl. J. Med. 345 (2001): 1655-1659.
2. Pastore et al. Renal cell carcinoma and interferon at the millennium. Cancer Invest. 19 (2001): 281-291.

## Interferon α + Vinblastine

## Indications:

- Advanced and metastatic renal cell carcinoma

## Schedule

- Interferon α 3 million units * 3 weekly day after day S.C
- Vinblastine 10 mg i.v. weekly

# SARCOMA

- Osteosarcoma

## Carboplatin / Etoposide

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1-4 | Carboplatin | 150 | 5% Glucose | 500 | 1 hr | I.V. |
| 1-4 | Etoposide | 150 | 0.9% NaCl | 1000 | 1 hr | I.V. |
| Repeat every 22 days for 6 cycles.<br>Etoposide from 200 mg onwards in 1000 ml 0.9% NaCl | | | | | | |

## References:

1. National Comprehensive Cancer Network 2012.
2. Winkler K. et al., Cancer Treat Res 62: 269, 1993.

Chapter 1

# Doxorubicin + Cisplatin Protocol

## Indications:

- To be used for osteosarcoma

## Doxorubicin + Cisplatin Schedule:

- Doxorubicin 25 mg/$m^2$ I.V. (bolus), day 1-3
- Cisplatin 100 mg/$m^2$ I.V. (cont inf), day 1
- To be repeated every 3 weeks (2 courses preoperative, follos\wed after surgery by 4 courses post operative).

## References:


1. National Comprehensive Cancer Network 2012.
2. Bramwell VH et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J. Clin. Oncol. 10 (1992): 1579-1591.
3. Lewis IJ et al; MRC BO06 and EORTC 80931 collaborators; European Osteosarcoma Intergroup. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J. Natl. Cancer Inst. 99 (2007): 112-128.

# Gemcitabine + Docetaxel Protocol

## Indications:

- To be used for osteosarcoma

## Gemcitabine + Docetaxel Schedule:

- Gemcitabine 675mg/$m^2$ I.V. (90 min inf) days 1+8
- Docetaxel 75-100 mg/$m^2$ I.V. (1 hr inf), day 8
- To be repeated every 3 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Navid F et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer 113 (2008): 419-425.

Chapter 1

# EWING'S SARCOMA

## VACA (Vincristine – Actinomycin D – Cyclophosphamide – Doxorubicin)

## Indications:

- Localized Ewing's sarcoma of bone

**VACA schedule** ● = i.v.

| Week | 1 | 4 | 7 | 10 | 13 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyclophosphamide, 1200 mg/m² i.v d1 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Actinomycin D, 0.5 mg/m² i.v d1-3 | | ● | | ● | | ● | | ● | | ● | | ● | | ● |
| Doxorubicin, 20 mg/m² i.v4h inf. d1-3 | ● | | ● | | ● | | ● | | ● | | ● | | ● | |
| Vincristine, 1.5mg/m² i.v (max. total 2mg) d1 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |

## VAIA (Vincristine – Actinomycin D – Ifosfamide – Doxorubicin)

## Indications:

- High – risk Ewing's sarcoma of bone

**VAIA schedule** ● = i.v.

| Week | 1 | 4 | 7 | 10 | 13 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ifosfamide, 2 g/m² i.v. d1-3* | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Actinomycin D, 0.5 mg/m² i.v d1-3 | | ● | | ● | | ● | | ● | | ● | | ● | | ● |
| Doxorubicin, 20 mg/m² i.v 4h inf. d1-3 | ● | | ● | | ● | | ● | | ● | | ● | | ● | |
| Vincristine, 1.5mg/m² i.v (max. total 2mg) d1 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |

* Ifosfamide will be given with Misna as protection

## VIDE (Vincristine – Ifosfamide – Doxorubicin - Etoposide )

## Indications:

- Induction chemotherapy in Ewing's sarcoma of bone ( experimental regimen )

VIDE schedule ● = i.v.

| Day | 1 | 2 | 3 | 3- week cycle for 6 courses |
|---|---|---|---|---|
| Vincristine, 1.5mg/m² i.v (max. total 2mg) | | ● | | |
| Ifosfamide, 3 g/m² i.v. infusion* | ● | ● | ● | |
| Doxorubicin, 20 mg/m² i.v infusion | ● | ● | ● | |
| Etoposide, 150 mg/m² i.v infusion | ● | ● | ● | |

* Ifosfamide with Misna uroprotection

## EVAIA Protocol

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1-3 | Doxorubicin | 20 | 0.9% NaCl | 250 | 4 hr | I.V. |
| 1, 22 | Vincristine | 1.5* | 0.9% NaCl | 100 | 10 minutes | I.V. |
| 1-3, 22-24 | Etoposide | 150 | 0.9% NaCl | 1000 | 1 hr | I.V. |
| 1-3, 22-24 | Ifosfamide | 2000 | 0.9% NaCl | 1000 | 1 hr | I.V. |
| 1-4, 22-25 | Mesna | 2000 | 0.9% NaCl | 500 | 24 hr | I.V. |
| 22, 23, 24 | Actinomycin D | 0.5** | ----- | ----- | Bolus | I.V. |
| To be repeated evry 43 days. | | | | | | |

## Notes:

1. Etoposide from 200 mg onwards in 1000 ml 0.9% NaCl
2. (*) Vincristine max. 2 mg total doses.
3. (**) Actinomycin D max. 1 mg total doses.
4. Caution: Cardiac toxicity of doxorubicin at cumulative doses $\geq$ 500 mg/m$^2$
5. Ample fluids.

## References:

1. Schmoll H.-J. et al., Kompendium Internistische Oncology, Springer, S. 2128, 1999.

# SOFT TISSUE SARCOMA

## Doxorubicin

## Indications:

- Palliation of advanced or metastatic soft tissue sarcoma

| **Doxorubicin schedule** | | **● = i.v.** |
|---|---|---|
| Day | 1 | 3- week cycle |
| Doxorubicin, 75 mg/m² i.v | ● | |

## Ifosfamide

## Indications:

- Palliation of advanced or metastatic soft tissue sarcoma

## Ifosfamide schedule

| D | Drug | Do, mg/m$^2$ | Di | **V, Ml** | **T** | **R** |
|---|---|---|---|---|---|---|
| 1-4 | Ifosfamide | 2000 | 0.9% NaCl | 500 | 24 hr | I.V. |
| Repeat every 22 days for 6 cycles. | | | | | | |

**OR**

- Ifosfamide 3000 mg/m$^2$ IV (4 hr inf), days 1-3
- To be repeated every 3 weeks.

**Notes:**

- Mesna 400 mg/m$^2$ bolus and 2000 mg/m$^2$ in parallel with Ifosfamide and over 12 hrs after Ifosfamide.
- Increased risk of CNS toxicity if albumin ≤ 3.5 g/dl.
- Ample fluids.

## References:

1. Van Oosterom AT et al. Results of randomized studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients Eur. J. Cancer 38: (2002): 2396-2406.
2. Antman K.H. et al., J Clin Oncol 7: 126ff, 1989.

# Ifosfamide – doxorubicin (IMA)

## Indications:

- Palliation of advanced, recurrent or metastatic soft tissue sarcoma

- Ifosfamide – doxorubicin schedule

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Ifosfamide | 5000 | 0.9% NaCl | 500 | 24 hr | I.V. |
| 1 | Doxorubicin | 50-75* | 0.9% NaCl | 250 | 1 hr | I.V. |
| Repeat every 22 days for 6 cycles (* 75 mg/m$^2$ with growth factor support) | | | | | | |

**Notes:**

- Mesna 1000 mg/m$^2$ bolus and 5000 mg/m$^2$ in parallel with Ifosfamide and 2500 mg/m$^2$ administered over 12 hr after Ifosfamide.
- Increased risk of CNS toxicity if albumin ≤ 3.5 g/dl.
- G-CSF administration: Day 2 -14
- Caution: Cardiac toxicity of Doxorubicin at cumulative doses ≥ 500 mg/m$^2$
- Ample fluids.

## References:

1. Schuette J et al. Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. The EORTC Soft Tissue and Bone Sarcoma Group. Eur. J. Cancer 26 (1990): 558-561.
2. Steward WP et al. Granulocyte-macrophage colony-stimulating factor allows safe escalation of dose-intensity of chemotherapy in metastatic adult soft tissue sarcomas: a study of the European Organization for Reasrch and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J. Clin. Oncol. 11 (1993): 15-21.

Chapter 1

# Imatinib Protocol

## Indications:

- To be used for gastrointestinal stroma.
- Unresectable or metastatic gastrointestinal stromal tumors

## Imatinib Schedule:

- Imatinib 400 mg once P.O. or b.i.d. P.O. daily
- Treatment should be continued indefinitely since interruption is generally followed by tumor progression.

## References:


1. National Comprehensive Cancer Network 2012.
2. Blanke CD et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J. Clin. Oncol. 26 (2008): 626-632.
3. DeMatteo RP et al; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal tumor: a randomized, double-blind, placebo-controlled trial. Lancet 373 (2009): 1097-1104.

# Paclitaxel Protocol

## Indications:

- Kaposi's sarcoma
- Anthracycline-resistant AIDS relaed Kaposi's sarcoma.
- Advanced Kaposi's sarcoma

## Paclitaxel Schedule:

- Paclitaxel 100 mg/$m^2$ I.V. (3 hr inf), day 1
- To be repeated every 2 weeks (with G-CSF support as required).

## References:

1. Strebbing J et al. Paclitaxel for anthracycline-resistant AIDS-related Kaposi's sarcoma: clinical and angiogenic correlations. Ann. Oncol. 14 (2003): 1660-1666.
2. Tulpule A et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi's sarcoma. Cancer 95 (2002): 147-154.

# Ifosfamide + Cisplatin Protocol

## Indications:

- Malignant mesodermal tumors.

## Ifosfamide + Cisplatin Schedule:

- Ifosfamide 1500 mg/m$^2$ I.V. (1 hr inf) day 1-4 with mesna uroprotection
- Cisplatin 20 mg/m$^2$ I.V. (short inf), day 1-4
- To be repeated every 3 weeks (adjuvant cycles)

## References:

1. Wolfson AH et al. A Gynecologic Oncology Group randomized phase III trial of whole abdominal irradiation (WAI) vs cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol. Oncol. 107 (2007): 177-185.

# Ifosfamide + Paclitaxel Protocol

## Indications:

- Malignant mesodermal tumors.

## Ifosfamide + Cisplatin Schedule:

- Ifosfamide 1200* or 1600 mg/m$^2$ I.V.(1 hr inf) day 1-3 with mesna uroprotection
- Paclitaxel 135 mg/m$^2$ I.V. mg/m$^2$ I.V. (3 hr inf) day 1
- To be repeated every 3 weeks (max 8 cycles)
- (*) For patients who had received prior radiation

## References:

1. Homesley HD et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J. Clin. Oncol. 25 (2007): 526-531.

# TESTICULAR CANCER

## BEP (Bleomycin – Etoposide – Cisplatin)

## Indications:

- Primary chemotherapy regimens for Germ Cell Tumors

**BEP schedule**

| **D** | **Drug** | **Do,** mg/m$^2$ | **Di** | **V,** Ml | T | R |
|---|---|---|---|---|---|---|
| 1-5 | Cisplatin | 20 | 0.9% NaCl | 500 | 30 mins | I.V. |
| 1-5 | Etoposide | 100 | 0.9% NaCl | 500 | 1 hr | I.V. |
| 1, 8, 15 or days (2, 9, 16) | Bleomycin | 30 (absolute) | ------- | ------- | Bolus | I.V. |
| Repeat every 22 days for 3-4 cycles. | | | | | | |

**Notes:**

- Etoposide from 200 mg onwards in 1000 ml 0.9% NaCl
- Cisplatin (only if GFR ≥ 60 ml/min):

Accompanying medication:
Premedication: 250 ml Mannit 20% or 40 mg Furosemide I.V.;
Postmedication: 2*1000 ml 0.9% NaCl I.V. and electrolyte balance.

## References:

1. National Comprehensive Cancer Network 2012.
2. Saxman SB, Finch D, Gonin R & Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: The Indiana University Experience. J Clin Oncol 1998; 16: 702-706.

# EP (Etoposide – Cisplatin)

## Indications:

- Primary chemotherapy regimens for Germ Cell Tumors

## EP schedule:

| D | Drug | Do, mg/m$^2$ | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1-5 | Cisplatin | 20 | 0.9% NaCl | 500 | 30 mins | I.V. |
| 1-5 | Etoposide | 100 | 0.9% NaCl | 500 | 1 hr | I.V. |
| Repeat every 21 days. | | | | | | |

**Notes:**

- Etoposide from 200 mg onwards in 1000 ml 0.9% NaCl
- Cisplatin (only if GFR ≥ 60 ml/min):

Accompanying medication:
Premedication: 250 ml Mannit 20% or 40 mg Furosemide I.V.;
Postmedication: 2*1000 ml 0.9% NaCl I.V. and electrolyte balance.

## References:

1. National Comprehensive Cancer Network 2012.
2. Xiao H, Mazumdar M, Bajorin DF, et al. Lon-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. J Clin Oncol 1997; 15: 2553-2558.

# BEP (Bleomycin – Etoposide – Cisplatin)

## Indications:

- Metastatic non – seminomatous germ cell tumors
- Metastatic seminomatous germ cell tumors
- Adjuvant therapy for stage 1 non – seminomatous germ cell tumors with vascular invasion

**BEP schedule (3 – day schedule with high dose etoposide)** **● = i.v.**

| Day | 1 | 2 | 3 | 8 | 15 | 3- week cycle |
|---|---|---|---|---|---|---|
| Bleomycin, 30 IU i.v. | ● | | | ● | ● | |
| Etoposide, 165mg/m² i.v infusion | ● | ● | ● | | | |
| Cisplatin, 50 mg/m² i.v infusion | ● | ● | | | | |

**BEP (5 – day schedule)** **● = i.v.**

| Day | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 3- week cycle |
|---|---|---|---|---|---|---|---|---|
| Bleomycin, 30 IU i.v. | ● | | | | ● | ● | | |
| Etoposide, 100mg/m² i.v infusion | ● | ● | ● | ● | ● | | | |
| Cisplatin, 50 mg/m² i.v infusion | ● | ● | ● | ● | ● | | | |

**BEP (3 – day schedule)** **● = i.v.**

| Day | 1 | 2 | 3 | 8 | 15 | 3- week cycle |
|---|---|---|---|---|---|---|
| Bleomycin, 30 IU i.v. | ● | | ● | ● | | |
| Etoposide, 120mg/m² i.v infusion | ● | ● | ● | | | |
| Cisplatin, 50 mg/m² i.v infusion | ● | ● | | | | |

# VIP / Salvage regimen

## Indications:

- Primary chemotherapy regimens for Germ Cell Tumors

| D | Drug | Do, mg/m² | Di | V, Ml | T | R |
|---|---|---|---|---|---|---|
| 1-5 | Cisplatin | 20 | 0.9% NaCl | 500 | 30 mins | I.V. |
| 1-5 | Etoposide | 75 | 0.9% NaCl | 1000 | 1 hr | I.V. |
| 1-5 | Ifosfamide | 1200 | 0.9% NaCl | 500 | 1 hr | I.V. |
| Repeat every 21 days. | | | | | | |

**Notes:**

- Mesna 120 mg/m² slow IV push before ifosfamide on Day 1, then Mesna 1200 mg/m² IV continuous infusion on Days 1-5.

- Cisplatin (only if GFR ≥ 60 ml/min):

Accompanying medication:

Premedication: 250 ml Mannit 20% or 40 mg Furosemide I.V.; Postmedication: 2*1000 ml 0.9% NaCl I.V. and electrolyte balance.

- Increased risk of CNS toxicity if albumin ≤ 3.5 g/dl.

## References:

1. National Comprehensive Cancer Network 2012.
2. Nichols CR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 1998; 16: 1287-1293.

# Carboplatin

## Indications:

- Stage IIB testicular seminoma.

| **Carboplatin schedule** | | **● = i.v.** |
|---|---|---|
| Day | 1 | 3- week cycle |
| Carboplatin (AUC7), i.v. infusion* | ● | |

* Carboplatin dose should be calculated by the formula:
Dose in mg = 7x (EDTA clearance +25), where EDTA clearance is in ml/minute.

## IPE (Ifosfamide – cisplatin – etoposide)

## Indications:

- Salvage therapy for relapsed germ cell tumors
- Metastatic non – seminomatous germ cell tumors (NSGCT)

| **IPE schedule** | | | | | | **● = i.v.** |
|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 3- week cycle |
| Ifosfamide, 1 g/m² i.v. inf. | ● | ● | ● | ● | ● | |
| Cisplatin, 20 mg/m² i.v infusion | ● | ● | ● | ● | ● | |
| Etoposide, 100mg/m² i.v infusion | ● | | ● | | ● | |

# VeIP / Salvage regimen

## Indications:

- Second-line or subsequent chemotherapy for metastatic Germ Cell Tumor

## VeIP schedule:

- Vinblastine 0.11 mg/kg I.V. on days 1 and 2
- Ifosfamide 1200 mg/m$^2$ I.V. on days 1-5
- Cisplatin 20 mg/m$^2$ I.V. on days 1-5
- Mesna 400 mg/m$^2$ I.V., given 15 minutes before first ifosfamide dose, then 1200 mg/m$^2$/day I.V. continuous infusion for 5 days OR 400 mg/m$^2$ every 8 hrs on days 1-5
- Repeat cycle every 21 days.

## References:

1. National Comprehensive Cancer Network 2012.
2. Loehre PJ Sr, Lauer R, Roth BJ, et al. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 1988; 109: 540-546.

# BRAIN TUMOR

| **ICE Ifosfamide – Carboplatin – Etoposide** | | | | **● = i.v.** |
|---|---|---|---|---|
| Day | 1 | 2 | 3 | |
| Ifosfamide, 750-1200 mg/m² i.v. | ● | ● | ● | |
| With mezna uroprotection | | | | |
| Carboplatin, 75 mg/m² i.v. | ● | ● | ● | |
| Etoposide, 75 mg/m² i.v. | ● | ● | ● | |

In anaplastic astrocytoma or anaplastic oligeostrocytoma you can give one of the following:

- Vincristine
- Methotrexate
- Procarbazine: 150 mg/m$^2$ P.O. daily divided into 3 doses (Repeat daily).
- Hydroyurea
- Cisplatin or Carboplatin

# CARCINOMA OF UNKNOWN PRIMARY

The selection of a possible therapy regimen should take into consideration the most probable localization and the histology of the primary.

**Paclitaxel + Carboplatin + Etoposide**

| | | | |
|---|---|---|---|
| Paclitaxel | 200mg/m² | i.v. (1 h inf) | d1 |
| Carboplatin | AUC = 6 | i.v. (20-30 min inf) | d1 |
| Etoposide | 50mg | p.o | d1,3,5,7,9 and |
| | 100mg | p.o | d2,4,6,8,10 |

To be repeated every 3 weeks

## Cisplatin – based combination chemotherapy

Cisplatin, vinblastine, bleomycin ± doxorubicin or cisplatin, etoposide ± bleomycin. Usual of cisplatin 20mg/m² i.v. days 1-5, etoposide 100mg/m² i.v. days 1-5, bleomycin 30 U/wk. if response after two courses at three week intervals, four courses were given.

**Docetaxel + Carboplatin**

| | | | |
|---|---|---|---|
| Docetaxel | 65mg/m² | i.v. | d1 |
| Carboplatin | AUC = 6 | i.v. | d1 |

To be repeated every 3 weeks (max 8 courses in stable or responding patients)

**TFL**

| | | | |
|---|---|---|---|
| Paclitaxel | 175mg/m² | i.v. (3 h inf) | d1 |
| 5-Fluorouracil | 350mg/m² | i.v. (30-60 min inf) | d1-3 |
| Folinic acid | 300mg | i.v. ( 30-60 min inf) | d1-3 |

To be repeated every 4 weeks

**VAC**

| | | | |
|---|---|---|---|
| Vincristine | 1.4mg/m² | i.v. | d1 |
| Doxorubicin | 50mg/m² | i.v. | d1 |
| Cyclophosphamide | 500mg/m² | i.v. | d1 |

To be repeated every 3 weeks

**Docetaxel +Cisplatin**

| | | | |
|---|---|---|---|
| Docetaxel | 100mg/m² | i.v. (1 h inf) | d1 |
| Cisplatin | 75mg/m² | i.v. (3 h inf) | d1 |

To be repeated every 3 weeks

# HEPATOCELLUALR CARCINOMA

**PIAF**

| | | | |
|---|---|---|---|
| Cisplatin | 20mg/m² | i.v. | d1- 4 |
| Doxorubicin | 40mg/m² | i.v. | d1 |
| 5-Fluorouracil | 400mg/m² | i.v. | d1- 4 |
| Interferon alpha | 5x10U/m² | i.v. | d1- 4 to |
| | | | be repeated every 3-4 weeks |

## Capecitabine:

- Capecitabine 1000 mg/m$^2$ P.O. bid on days 1-14
- Repeat cycle every 21 days.
- Dose may be reduced to 825-900 mg/m$^2$ P.O. bid on days 1-14. This dose reduction may decrease the risk of toxicity without compromising clinical efficacy.

## Doxorubicin Protocol

- Doxorubicin 60 mg/m$^2$ IV, day 1
- To be repeated every 3 weeks.

## References:

1. Gish RG et al. Pahse III randomized contolled trial comparing the syrvival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. J. Clin. Oncol. 25 (2007): 3069-3075.
2. Lai Cl et al. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer 62 (1988): 479-483.

# GEMOX Protocol

- Gemcitabine 1000 mg/m$^2$ IV, day 1
- Oxaliplatin 100mg/m$^2$ IV (2 hr inf), day 1
- To be repeated every 2 weeks.

## References:

1. Louafi S et al. Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): results of a phase II study. Cancer 109 (2007): 1384-1390.

# Capecitabine + Cisplatin Protocol

- Capecitabine 2000 mg/m$^2$ PO, day 1-14
- Cisplatin 60 mg/m$^2$ IV, day 1
- To be repeated every 3 weeks (until disease progression or unacceptable toxicity).

## References:

1. Lee JO et al. Combination chemotherapy with capecitabine and cisplatin for patients with metastatic hepatocellular carcinoma. Ann. Oncol. 20 (2009):1402-1407.

# NEUROENDOCRINE TUMORS

**Doxorubicin**

| | | | |
|---|---|---|---|
| Doxorubicin | 60mg/m² | i.v. (bolus) | d1 |

**5-Fluorouracil**

| | | | |
|---|---|---|---|
| 5-Fluorouracil | 500mg/m² | i.v. (bolus) | d1-5 |

**Etoposide + cisplatin**

| | | | |
|---|---|---|---|
| Etoposide | 130mg/m² | i.v. (24h inf) | d1-3 |
| Cisplatin | 45mg/m² | i.v. (24h inf) | d2-3 |

To be repeated every 4 weeks (max 6 cycle)

# THYMOMA/ THYMIC CARCINOMA

## Thymoma

**CAP**

| | | | |
|---|---|---|---|
| Cisplatin | 50 mg/m² | i.v. (1 h inf) | d1 |
| Doxorubicin | 50 mg/m² | i.v. (bolus) | d1 |
| Cyclophosphamide | 500 mg/m² | i.v. (bolus) | d1 |

To be repeated every 3 weeks (2-4 cycles, followed by radiotherapy as induction therapy).

## CAP with Prednisone

- Cisplatin 30 mg/m2 on day 1-3
- Doxorubicin 20 mg/m$^2$/d, I.V. continuous infusion on day 1-3
- Cyclophosphamide 500 mg/m$^2$ I.V. on day 1
- Prednisone 100 mg/day on day 1-5
- Administered every 3 weeks

## References:

1. National Comprehensive Cancer Network 2012.

**ADOC**

| | | | |
|---|---|---|---|
| Doxorubicin | 40 mg/m² | i.v. (bolus) | d1 |
| Cisplatin | 50 mg/m² | i.v. (1 h inf) | d1 |
| Vincristine | 0.6 mg/m² | i.v. (bolus) | d3 |
| Cyclophosphamide | 700 mg/m² | i.v.(bolus) | d4 |

To be repeated every 4 weeks (3-6 cycles, as induction therapy).

**PE**

| | | | |
|---|---|---|---|
| Cisplatin | 60 mg/m² | i.v.(1 h inf) | d1 |
| Etoposide | 120 mg/m²/d | i.v.(30 min inf) | d1-3 |

To be repeated every 3 weeks.

**VIP**

| | |
|---|---|
| Etoposide | 75 mg/m$^2$ on day 1-4 |
| Ifosfamide | 1.2 g/m$^2$ on day 1-4 |
| Cisplatin | 20 mg/m$^2$ on day 1-4 |
| Administered | every 3 weeks |

## References:

1. National Comprehensive Cancer Network 2012.

**Carboplatin/ Paclitaxel (preferred for thymic carcinoma)**

| |
|---|
| Carboplatin AUC 6 |
| Paclitaxel 225 mg/m$^2$ |
| Administered every 3 weeks |

## References:

1. National Comprehensive Cancer Network 2012.

**Ifosfamide (Second-line)**

| | | | | |
|---|---|---|---|---|
| Ifosfamide | 1500 mg/m² | i.v. (30 min inf) | d1-5 | with mesna uroprotection |

To be repeated every 3 weeks.

## References:

1. National Comprehensive Cancer Network 2012.

# THYROID CARCINOMA

**Doxorubicin**

| | | | |
|---|---|---|---|
| Doxorubicin | 60 mg/m² | i.v. (bolus) | d1 |

To be repeated every 3 weeks.

## Combination Chemotherapy

**Doxorubicin + cisplatin**

| | | | |
|---|---|---|---|
| Doxorubicin | 60 mg/m² | i.v. (bolus) | d1 |
| Cisplatin | 40 mg/m² | i.v. (30 min inf) | d1 |

To be repeated every 3 weeks

# BONE METASTASIS

Pamidronate disod 90 mg i.v. monthly

# Chapter 2

# PEDIATRIC ONCOLOGY

# NEUROBLASTOMA

### CDEC

| | | | |
|---|---|---|---|
| Cisplatin | 60mg/m² | I.V. (6 h inf) | d0 |
| Doxorubicin | 30 mg/m² | I.V. | d2 |
| Etoposide | 100 mg/m² | I.V. (1 h inf) | d2+5 |
| Cyclophosphamide | 900 mg/m² | I.V. | d3+4 |

### CPM / DOX

| | | | |
|---|---|---|---|
| Cyclophosphamide | 150mg/ m² | I.V. or P.O | for 7 d |
| Doxorubicin | 35mg/m² | i.v. | d1 |

### CPM / CDDP/ DOX

| | | | |
|---|---|---|---|
| Cyclophosphamide | 150mg/ m² | I.V. or P.O | for 7 d |
| Cisplatin | 90mg/m² | I.V. (8 h inf) | d1 |
| Doxorubicin | 35mg/m² | I.V. | d1 |

## CDDP/ ETOP

| | | | |
|---|---|---|---|
| Cisplatin | 90mg/m² | I.V. (8 h inf) | d1 |
| Etoposide | 150mg/m² | I.V. (cont inf) | over 3 d |

### CPM / ETOP

| | | | |
|---|---|---|---|
| Cyclophosphamide | 150mg/ m² | I.V. or P.O | for 7 d |
| Etoposide | 150mg/m² | I.V. (cont inf) | over 3 d |

# RETINOBLASTOMA

**CADO**

| | | | |
|---|---|---|---|
| Cyclophosphamide | 20-40 mg/kg* | I.V. (1 h inf) | d1 |
| Doxorubicin | 0.67 mg/kg | I.V. (1 h inf) | d1-3** |
| Vincristine | 0.05 mg/kg | I.V. (bolus) | d1 |

* Week 0 = 40 mg/kg
Weeks 3, 6, 9, 12, 15, 18, 21= 20mg/kg
Weeks 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57=30 mg/kg

** stopped after week 21

**Etoposide + carboplatin**

| | | | |
|---|---|---|---|
| Etoposide | 100mg/ m² | I.V. (1 h inf) | d 1- 5 |
| Carboplatin | 160mg/ m² | I.V. (1 h inf) | d 1- 5 |
| To be repeated every 3-4 weeks. | | | |

**VEC**

| | | | |
|---|---|---|---|
| Carboplatin | 560mg/m²* | I.V. (1 h inf) | d 1 |
| Etoposide | 150mg/m²* | I.V. (1 h inf) | d 1+**2** |
| Vincristine | 1.5mg/m²* | I.V. (bolus) | d 1 |
| | (max 2 mg) | | |

To be repeated every 4 weeks.

* For patients ≤ 36 months of age 18.6mg/kg, 5mg/kg, and 0.05mg/kg, respectively.

# Cyclophosphamide + Vincristine

| | | | |
|---|---|---|---|
| Cyclophosphamide | 300mg/m² | I.V | wk x 6, thereafter |
| | 200mg/m² | I.V | wk for one year |
| Vincristine | 1.5mg/m² | I.V. | wk x 6, thereafter |
| | 1.0mg/m² | I.V | wk for one year |

# HEPATOBLASTOMA

**Plado (SIOPEL – 1)**

| | | | |
|---|---|---|---|
| Cisplatin | 80mg/m² | I.V. (count inf) | d1 |
| Doxorubicin | 30mg/m² | I.V. (count inf) | d2+3 |

To be repeated every 3 weeks (4-6 courses followed by an attempt of resection).

## Cisplatin + 5-Fluorouracil +Vincristine (Intergroup Hepatoma study)

| | | | |
|---|---|---|---|
| Cisplatin | 90mg/m²* | I.V. (6 h inf) | d1 or |
| | 3mg/kg** | I.V. (6 h inf) | d1 |
| Vincristine | 1.5mg/m² | I.V. (bolus) | d2 |
| 5-Fluorouracil | 600mg/m² | I.V. (bolus) | d2 |

To be repeated every 3 weeks.

* ≥ 1year of age.

** < 1 year of age.

## IPA/PA-CI (GPOH HB89)

**IPA**

| | | | |
|---|---|---|---|
| Ifosfamide | 500mg/m² | I.V. (bolus) | d1 and |
| | 3000mg/m² | I.V. (count inf) | d1-3 |
| | | with mesna uroprotection | |
| Cisplatin | 20mg/m²* | I.V. | d4-8 |
| Doxorubicin | 60mg/m² | I.V. (count inf) | d9+10 |

To be repeated every 3 weeks for 2 courses, then re-evaluation for respectability. If resection was not possible, two more courses of chemotherapy:

**PA-CI**

| | | | |
|---|---|---|---|
| Cisplatin | 90mg/m² | I.V. (4 h inf) | d1 |
| Doxorubicin | 80mg/m² | I.V. (count inf) | d2-5 |

# SOFT TISSUE SARCOMAS (incl. Kaposi's Sarcoma and Gynecological Sarcomas)

**Main histological groups:**

Fibrosarcoma.
Liposarcoma
Leiomyosarcoma.
Rhabdomyosarcoma.
Endothelial sarcomas of blood and lymph vessels (angiosarcoma, lympangiosarcoma, kaposi's sarcoma)
Perivascular sarcoma (hemangiopericytoma).
Synovial sarcoma
Mesothelial sarcomas (see mesothelioma).
Neural sarcomas (malignant schwannoma, see also neuroblastoma, brain tumor of mesenchymal origin)
Spindle – cell sarcoma
Others.

**Doxorubicin**

| | | | |
|---|---|---|---|
| Doxorubicin | ≥70mg/kg | I.V. (short inf) | d1 |

To be repeated every 3 weeks.

**Ifosfamide**

Various schedules, e,g. " standard – dose"

| | | | |
|---|---|---|---|
| Ifosfamide | 5000mg/m² (max 8000mg) | I.V. (24 h inf) with mesna uroprotection | d1 |

To be repeated every 3 weeks.

**Ifosfamide + doxorubicin**

| | | | |
|---|---|---|---|
| Ifosfamide | 5000mg/m² | I.V.(24 h inf) | d1 |

With mesna uroprotection

| | | | |
|---|---|---|---|
| Doxorubicin | 50-75mg/m²* | I.V. (short inf) | d1 |

To be repeated every 3 weeks. *(75mg/m² with growth factor support).

OR

| | | | |
|---|---|---|---|
| Ifosfamide | 2000mg/m² | I.V. (2 h inf) | d1-5 |

With mesna uroprotection

| | | | |
|---|---|---|---|
| Doxorubicin | 25mg/m² | I.V. (cont inf) | d1-3 |

To be repeated every 3 weeks. (With growth factor support as required).

**Ifosfamide + epirubicin**

| | | | |
|---|---|---|---|
| Epirubicin | 60 mg/m² | I.V. (short inf) | d1+2 |
| Ifosfamide | 1800 mg/m² | I.V. (1 h inf) | d1-5 |

With mesna uroprotection

To be repeated every 3 weeks. (With growth factor support, five cycles as adjuvant therapy).

## MAID

| | | | |
|---|---|---|---|
| Doxorubicin | 15mg/m²/d | I.V. (cont inf) | d1-4 |
| Dacarbazine | 250mg/m²/d | I.V. (cont inf) | d1-4 |
| Ifosfamide | 2000-2500mg/m²/d | I.V. (cont inf) | d1-3 |

With mesna uroprotection

To be repeated every 3 weeks.

**Imatinib mesylate**

| | | | |
|---|---|---|---|
| Imatinib mesylate | 400-600 mg | P.O | daily or |
| | 300-400 mg | b.i.d. P.O. | daily |

**ABV**

| | | | |
|---|---|---|---|
| Doxorubicin | 40 mg/m² | I.V. (bolus) | d1 |
| Bleomycin | 15 mg/m² | I.V. (bolus) | d1+15 |
| Vinblastine | 6 mg/m² | I.V. (bolus) | d1 |

Or

| | | | |
|---|---|---|---|
| Doxorubicin | 10 (-20) mg/m² | I.V. (bolus) | d1 |
| Bleomycin | 10 mg/m² | I.V. (bolus) | d1 |
| Vinblastine | 1.4 mg/m² (max 2 mg) | I.V. (bolus) | d1 |

To be repeated every 2 weeks.

# WILMS TUMOR (NEPHROBLASTOMA) FOR PRE – TREATED CASES

**LOW RISK TUMORS**

Mesoblastic nephroma
Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma

**INTERMEDIATE RISK TUMORS**

Nephroblastoma – epithelial type
Nephroblastoma – stromal type
Nephroblastoma – mixed type
Nephroblastoma – regressive type
Nephroblastoma – focal anaplasia

**HIGH RISK TUMOR**

Nephroblastoma – blastomal type
Nephroblastoma – diffuse anaplasia
Clear cell sarcoma of the kidney
Rhabdoid tumor of the kidney

# FOR PRIMARY NEPHROBLASTOMY CASES

**LOW RISK TUMORS**

Mesoblastic nephroma
Cystic partially differentiated nephroblastoma

**INTERMEDIATE RISK TUMORS**

Non – anaplastic nephroblastoma and its variants
Nephroblastoma – focal anaplasia

**HIGH RISK TUMOR**

Nephroblastoma – diffuse anaplasia
Clear cell sarcoma of the kidney
Rhabdoid tumor of the kidney

# Relapsed and poor risk Wilms' tumor

**ICE Protocol (Selected schedules in the therapy of Malignant Tumors 2011)**
**ICE schedule:**
Ifosfamide 1800 mg/$m^2$, I.V. with mesna uroprotection, days 1-5
Carboplatin 400 mg/$m^2$, I.V. days 1+2
Etoposide 100 mg/$m^2$, I.V. days 1-5
To be repeated every 3 weeks.

# LEUKEMIA

## 1. ACUTE LYMPHOBLASTIC LEUKEMIA:

**Therapy for Standard-Risk ALL**

**Induction (1 month):**

Oral dexamethasone for 28 days (6 mg/m2/day in three divided doses), IV vincristine (1.5 mg/m2 on days 0, 7, 14 and 21), intramuscular pegylated L-asparaginase (2,500 units/m2, on day 4), (pegylated asparaginase can also be given intravenously using the same dose over 2 hours) and at time of initial lumbar puncture age-adjusted intrathecal cytarabine (age 1 to less than 2 years 30 mg; age 2 to less than 3 years 50 mg; age 3 years and older 70 mg) and intrathecal methotrexate (age 1 to less than 2 years, 8 mg; age 2 to less than 3 years, 10 mg; older than 3 years, 12 mg on day 14)

**Consolidation (1 month):**

Oral 6-mercaptopurine (75 mg/m2/d on days 1–28 of consolidation), IV vincristine (1.5 mg/m2 on day 1) and age-adjusted (see above) intrathecal methotrexate on days 1, 8 and 15 for patients without CNS disease at diagnosis.

**Interim maintenance:**

IV vincristine 1.5 mg/m2 (max dose 2 mg) on days 1, 11, 21, 31 and 41, IV methotrexate starting dose of 100 mg/m2/dose over 10–15 minutes on day 1 thereafter escalate by 50 mg/m2/dose on days 11, 21, 31 and 41 (discontinue escalation and resume at 80% of last dose if there is a delay because of myelosurpression or mucositis). Age-adjusted intrathecal methotrexate (see Induction) on day 31.

**Delayed intensification (2 months):**

Oral dexamethasone in all patients (10 mg/m2/d on days 1–7 and 14–21 days), IV vincristine (1.5 mg/m2 on days 0, 7 and 14), intramuscular or intravenous pegylated L-asparaginase (2,500 u/m2 on day 4), doxorubicin (25 mg/m2, IV push, on days 0, 7 and 14), IV cyclophosphamide (1,000 mg/m2 over 30 minutes on day 28), oral 6-thioguanine (60 mg/m2/day on days 28 to 41), cytarabine (75 mg/m2/day, IV push, on days 29–32 and 36–39) and age-adjusted intrathecal methotrexate (see Induction) on day 28.

### Maintenance (Female 20 months; Male: 32 months):

Dexamethasone (6 mg/m2/day on days 0 to 4, 28 to 32 and 56 to 60), oral mercaptopurine (75 mg/m2/day on days 0 to 83), IV vincristine (1.5 mg/m2 on days 0, 28 and 56), weekly oral methotrexate (20 mg/m2 beginning on day 7 of each course) and age-adjusted intrathecal methotrexate (see Induction) on day 0 of each course.

## High-risk Pre-B Cell ALL Protocol for Rapid Early Responders (RER) and for Slow Early Responders (SER)

**Induction:**
Prednisone 60 mg/m2/day PO for 28 days
Vincristine 1.5 mg/m2/week IV, days 1, 8, 15, 22
Daunomycin 25 mg/m2/week IV, days 1, 8, 15, 22
PEG Asparaginase 2,500 units/m2/day IM, day 4
Cytarabinea Age-adjusted IT, day 0
Methotrexatea Age-adjusted IT, day 8

**Consolidation (9 weeks):**
Cyclophosphamide 1,000 mg/m2/day IV, days 0, 28
Cytarabine 75 mg/m2/day IV, days 1–4, 8–11, 29–32, 36–39
Mercaptopurine 60 mg/m2/day PO, days 0–13 and days 28–41
Vincristine 1.5 mg/m2/day IV, days 14, 21, 42, 49
PEG asparaginase 2,500 units/m2 IM days 14, 42
Methotrexate Age adjusted IT, days 1, 8, 15, 22

**Interim Maintenance 1 (7 Weeks):**
Vincristine 1.5 mg/m2 per day IV days 0, 10, 20, 30, 40 Interim Maintenance I
Methotrexate 100 mg/m2/day IV days 0, 10, 20, 30, 40, (7 Weeks)
Escalate by 50 mg/m2 per dose
PEG Asparaginase 2,500 units/m2 IM days 1, 21
Methotrexate Age-adjusted IT days 0, 30

## Delayed Intensification I (8 weeks)

**Reinduction (4 weeks):**
Dexamethasone 10 mg/m2/day PO, days 0–7, 14–20
Vincristine 1.5 mg/m2/day IV, days 0, 7, 14
Doxorubicin 25 mg/m2/day IV, days 0, 7, 14
PEG Asparaginase 2,500 units/m2/day IM, day 3,
Methotrexate Age-adjusted IT day 0

**Reconsolidation (4 weeks)**
Cyclophosphamide 1,000 mg/m2/day IV day 28
Thioguanine 60 mg/m2/day PO days 28 to 41
Cytarabine 75 mg/m2/day SC or IV days 29 to 32, 36 to 39
Methotrexate Age-adjusted IT days 28, 35
Vincristine 1.5 mg/m2 IV days 42, 49
PEG Asparaginase 2,500 units/m2 IM day 42

## For SER only give a second Interim Maintenance (for 7 weeks same as interim maintenance 1) and a second delayed intensification (for 8 weeks same as delayed intensification 1):

**Maintenance (12 weeks)**
Vincristine 1.5 mg/m2/day IV days 0, 28, 56
Prednisone 40 mg/m2/day PO days 0 to 4, 28–32, 56–60
Mercaptopurine 75 mg/m2/day PO days 0–83
Methotrexate 20 mg/m2/day PO days 7, 14, 21, 28 (hold cycles 1–4 when receiving IT
Methotrexate), 35, 42, 49, 56, 63, 70, 77
Methotrexate Age-adjusted IT day 0 in addition on day 28 cycles 1–4 in RER ONLY

**Notes:**
*RER (Day 7 Bone Marrow, 25% Blasts).
**SER-Augmented Regimen (Day 7 Bone Marrow .25% Blasts).
The doses are age adjusted: IT methotrexate age 1 to 1.9 yrs 8 mg; age 2 to 2.9 years 10 mg; age.3 years 12 mg, IT cytarbine age 1 to 1.9 yrs 30 mg, age 2 to 2.9 years 50 mg, age .3 years 70 mg.
The cycles of maintenance are repeated until the duration of therapy beginning with the first interim maintenance period reaches 2 years for girls and 3 years for boys.
During the first 2 weeks of consolidation therapy patients with central nervous system disease at diagnosis receive 2,400 cGy to the cranium in 12 fractions and 600 cGy to the spinal cord in 3 fractions. Patients with testicular disease at diagnosis receive 2,400 cGy bilateral testicular radiations in 8 fractions during consolidation therapy.
Patients with central nervous system disease at diagnosis do not receive intrathecal methotrexate on days 15 and 22 of consolidation therapy.
Abbreviations: IV, intravenously; PO, orally; IT, intrathecally; SQ, subcutaneously; IM, intramuscularly.

**References:**
1. Modified from: Siebel NL Stenherz PG, Harland HN, et al. Early post induction intensification therapy improves survival for children and adolescents with high risk acute lymphoblastic leukemia: a report from the Children's Oncology Group Blood 2008; 111:2548–2555.

## Treatment of Lesser Risk B-Lineage ALL

**Induction (weeks 1–4)**

Vincristine 15 mg/m2 IV on days 1, 8, 15 and 22

Prednisone 40 mg/m2 in three divided doses on days 1 to 28

L-asparaginase 6,000 units/m2 IM on days 2, 5, 8, 12, 15, 19

Intrathecal methotrexate therapy is age-adjusted (age 1 to 1.9 years 8 mg; 2 to 2.9 years 10 mg and > 3 years 12 mg) on days 1 and 22. Additional doses are given on days 8 and 15 when CNS 2 status is present.

**Consolidation (weeks 5–24)**

Methotrexate IV 1 gram/m2 as 24 hour infusion on weeks 7, 10, 13, 16, 19 and 22 with delayed leukovorin rescue (10 mg/m2) orally or IV every 6 hours for five doses beginning 48 hours after start of methotrexate infusion

6 mercaptopurine 50 mg/m2 orally daily on weeks 5–24

Intrathecal methotrexate (age-adjusted as above) on weeks 10, 13, 16, 19 and 22

Vincristine 1.5 mg/m2 IV on weeks 8 and 9 and weeks 16 and 17

Prednisone 40 mg/m2 orally in three divided doses for 7 days on weeks 8 and 16

**Maintenance (weeks 25–130)**

6 mercaptopurine 75 mg/m2 orally daily on weeks 25–130

Methotrexate 20 mg/m2 IM weekly on weeks 25–130 (half dose on days of intrathecal methotrexate)

Vincristine 1.5 mg/m2 IV weekly on weeks 25 and 26, 41 and 42, 57 and 58, 73 and 74, 89 and 90, 105 and 106.

Prednisone 40 mg/m2 for 7 days orally on weeks 25 to 26, 41 to 42, 57 to 58, 73 to 74, 89 to 90 and 105 to 106.

Intrathecal methotrexate (age-adjusted as above) is given every 12 weeks (weeks 25, 33, 41, 49, 57, 65, 73, 81, 89, 97 and 105)

## References:

1. Chauvenet AR, Martin PL, Devidas M, et al. Antimetabolite therapy for lesser-risk B-lineage acute lymphoblastic leukemia of childhood: a report from the Children's Oncology Group. Blood 2007;110:1105–1111.

## Protocol for B-Cell ALL and B-cell NHL with Marrow Involvement with or without CNS Involvement (LMB 89 Protocol)

**Reduction Phase**

COP

Cyclophosphamide 300 mg/m2 IV, day 1

Vincristine 1 mg/m2 (maximum dose, 2 mg) IV, day 1

Prednisone 60 mg/m2/day PO or IV, days 1–7

Methotrexate (MTX) and hydrocortisone (HC) 15 mg IT, days 1, 3 and 5 (dose adjusted for patients < 3 years of age)*

Ara-C 30 mg IT, days 1, 3 and 5 (dose adjusted for patients < 3 years of age)*

Folinic acid 15 mg/m2 q6h PO, days 2 and 4

## Induction: 2 courses, COPADM1 and COPADM2 started on day 8 after first day of reduction (COP) phase

**COPADM1:**

Vincristine 2 mg/m2 (maximum dose, 2 mg) IV, day 1

MTX high dose (HD) 8 g/m2 (over 4 hours) IV, day 1

Folinic acid 15 mg/m2 PO every 6 h312 doses, days 2–4 MTX level at 72 hours, < 0.1 μmol/l

MTX and HC 15 mg IT days 2, 4 and 6 (dose adjusted for patients < 3 years of age)*

Ara-C 30 mg IT, days 2, 4 and 6 (dose adjusted for patients < 3 years of age)

Cyclophosphamide 500 mg/m2/day IV, days, 2–4 (in 2 injections per day every 12 h and hydration)

Adriamycin 60 mg/m2 IV, day 2

Prednisone 60 mg/m2 PO or IV, days 1–6

**COPADM2 (after hematologic recovery):**

Same as COPADM1 except

Cyclophosphamide Doses doubled (1 g/$m^2$/day, always in 2 injections per day at 12 h intervals)

Second vincristine Day 6

## Consolidation: 2 courses of CYVE (after hematologic recovery)

**CYVE**

Cytarabine (Ara-C) 50 mg/m2/12-hour continuous infusions (hours 1–12), days 1–5

Cytarabine HD 3 g/m2/day (in 3 hours) IV (hours 12–15), days 1–4

VP16 200 mg/m2/day (in 2 hours) IV (hours 15–17), days 1–4

## Maintenance 4 courses monthly in succession

**Course 1**

Prednisone 60 mg/m2 PO in 2 divided doses, days 1–5
MTX HD 8 g/m2 (in 4 hours) IV, day 1
Folinic acid 15 mg/m2 every 6 hours IV, days 2–4
MTX IT and HC 15 mg IT, day 2 (doses adjusted for patients < 3 years of age)*
Ara-C 30 mg IT, day 2 (doses adjusted for patients < 3 years of age)*
Cyclophosphamide 500 mg/m2/day IV, days 1 and 2 (in 2 divided doses every 12 h per day)
Adriamycin 60 mg/m2 IV, day 2
Vincristine 2 mg/m2 (maximum dose, 2 mg) IV, day 1

Age-adjusted doses for intrathecal use (triple intrathecal).

| Age | MTX | HC |
|---|---|---|
| <1 year | 8 mg | 8 mg |
| 1 year | 10 mg | 10 mg |
| 2 years | 12 mg | 12 mg |
| >3 years | 15 mg | 15 mg |

Cranial irradiation 2,400 cGy to commence on day 8 in case of Initial meningeal involvement (except in case of isolated compression of spinal cord)

**Course 2 (after hematologic recovery)**

Cytarabine 100 mg/m2/day SC, days 1–5 (in 2 injections q12h)
VP16 150 mg/m2/day IV, days 1–3 (over 2 hours)

**Course 3 (after hematologic recovery)**

Same as course l except without MTX HD and without IT

**Course 4 (after hematologic recovery)**

Same as course 2

## Notes:

1. (*): Age-adjusted doses for intrathecal use (triple intrathecal).
2. Abbreviations: MTX and HC, methotrexate and hydrocortisone; Ara-C, cytarabine, cytosine arabinoside; IT, intrathecal; HD, high dose; SC, subcutaneous.

## References:

1. 66Patte C, Auperin A, Michon J, et al. The Societe Francaise d' Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001;97:3370–3379.

# PROTOCOL FOR T-CELL ALL

## Induction

**4 Weeks:**
Vincristine 1.5 mg/$m^2$ weekly
Prednisone 40 mg/$m^2$/day for 28 days
Doxorubicin 30 mg/$m^2$ on days 5 and 6
IT Ara-C (dosed by age) on days 5 and 19
MTX 4 gm/$m^2$ on day 5 eight hours after 2nd dose of doxorubicin with leukovorin rescue beginning at hour 36

**CNS treatment 3 Weeks:**
Cranial XRT 1,800 cGy with IT medications 4 doses during cranial radiation

**Intensification 6–9 months:**
Prednisone 120 mg/m2/day for 5 days every 3 weeks
Doxorubicin 30 mg/$m^2$ every 3 wk until cumulative dose of
Doxorubicin reaches 360 mg/$m^2$ and then substitute methotrexate as in continuation
6-mercaptopurine 50 mg/$m^2$/d po for 14 days
L-asparaginase 25,000 IU/$m^2$ every wk for 20 wks
Vincristine 2.0 mg/m2 IV every 3 weeks
IT Ara-C and methotrexate every 18 weeks

**Continuation until 2 yrs (continual complete remission):**
Prednisone 120 mg/m2/d for 5 days
6-mercaptopurine 50 mg/m2/d po for 14 d
Vincristine 2.0 mg/m2 IV every 3 wk
Methotrexate 30 mg/m2 IV weekly
IT Ara-C and methotrexate every 18 weeks
*Every 3 weeks

IT doses: IT Ara-C 15 mg < 1 year, 1–2 years 20 mg, 2–3 years 30 mg, ≥ 3 years 40 mg. Methotrexate 8 mg ages 1–2, 10 mg ages 2–3, 12 mg ages > 3 years.

## References:

1. Goldberg JM, Silverman LB, Levy DE, et al. Childhood T cell acute lymphoblastic leukemia. The Dana-Farber Cancer Institute. Acute Lymphoblastic Leukemia Consortium experience. J Clin Oncol 21;2003:3616–3622.

## Memorial Sloan-Kettering-New York 2 Protocol for Acute Lymphoblastic Leukemia Relapse

**Induction:**

Day 0: cytosine arabinoside 20, 30, 50, or 70 mg

Days 0, 1: daunorubicin 60 mg/m2/day 3 2 or daunorubicin 120 mg/$m^2$ over 48 hours continuous infusion

Day 2: cyclophosphamide 1200 mg/$m^2$ IV Days 2, 9, 16, 23: vincristine 1.5 mg/$m^2$ IV Days 2–23: prednisone 60 mg/$m^2$/day PO and 9-day tapering dose

Day 4 and every Monday, Wednesday and Friday there after: L-asparaginase 6,000 units/$m^2$/day IM

Days 15, 22: methotrexate 6, 8, 10, or 12 mg IT for ages ,1, 1–2, 2–3 and .3 years, respectively

**Consolidation:**

(begins on the nearest Monday to day 28 or when ANC .500/$mm^3$ and platelet count .100,000/$mm^3$)

Days 28, 29: cytosine arabinoside 3,000 mg/$m^2$ over 3 hours IV

Days 28, 30, 32, 37, 39, 42, 44, 46, etc. until the beginning of maintenance: L-asparaginase 6,000 units/$m^2$/day IM

Day 31: methotrexate 150 mg/$m^2$ IV over 4 hours

Days 32 and 39: vincristine 1.5 mg/$m^2$ IV

Days 32–39: prednisone 180 mg/$m^2$/day PO

**First maintenance:**

(day 56 of consolidation is day 0, begins with ANC .1000/$mm^3$ and platelet count.100,000/$mm^3$)

Days 0, 7, 15, 22: methotrexate IT

Days 0–3: 6-mercaptopurine 300 mg/$m^2$/day PO

Day 4: cyclophosphamide 600 mg/m2 IV days 4, 11, 18, 25, 32, 39, 46, 53, 60: L-asparaginase 25,000 units IM

Days 11, 18, 25: vincristine 1.5 mg/$m^2$ IV

Days 18 to 25: prednisone 180 mg/$m^2$/day PO

Day 25: methotrexate 150 mg/$m^2$ IV over 4 hours IT for ages, 1, 1–2, 2–3, 3 years, respectively

Days 40, 41: daunorubicin 20 mg/$m^2$/day IV or daunorubicin 40 mg/$m^2$ over 48 hours infusion intravenous

Days 42–44: cytosine arabinoside 100 mg/$m^2$/day, 72-hour continuous infusion

Days 42–44: thioguanine 40 mg/$m^2$/day PO every 12 hours 3, 6

**Subsequent maintenance cycles**

Day 0: methotrexate IT

Days 0–3: 6-mercaptopurine 300 mg/m$^2$/day PO, cyclophosphamide 1,200 mg/m2 IV

Days 11, 18, 25: vincristine 1.5 mg/m$^2$ IV

Days 18–25: prednisone 180 mg/m$^2$/day PO

Day 25: methotrexate 200 mg/m$^2$ IV over 4 hours, escalate dose by 50 mg/m$^2$ each subsequent cycle until mucositis or ANC <500/mm$^3$ occurs

Days 40, 41: daunorubicin 20 mg/m2/day IV or daunorubicin 40 mg/m$^2$ over 48 hour

Infusion intravensously or dactinomycin 750 ug/m$^2$ IV

Day 41 (1 day only instead of 2-day Daunorubicin) once the limit of anthracycline has been reached

Days 42–44: cytosine arabinoside 100 mg/m$^2$/day, 72-hour continuous infusion

Days 42–44: thioguanine 40 mg/m$^2$/day PO every 12 hours 3 6

Duration of maintenance therapy: 2 years

- **Abbreviations: IT, intrathecal; IV, intravenous; PO, oral; IM, intramuscular; CNS, central nervous system; ANC, absolute neutrophil count.**

## References:

2. Steinherz PG, Redner A, Steinherz L, et al. Development of a new intensive therapy for acute lymphoblastic leukemia in children at increased risk of early relapse. Cancer 1993; 72:3120–3130, with permission.

## Alternate Induction for Recurrent Acute Lymphoblastic Leukemia

| Drug and Dosage | Day Number |
|---|---|
| Block 1 | |
| Vincristine, 1.5 mg/m2 IV | 1, 8, 15 and 22 |
| Prednisone, 40 mg/m2/d PO | 1–29 |
| PEG-asparaginase, 2,500 U/m2 IM | 2, 9, 16 and 23 |
| Doxorubicin, 60 mg/m2 IV | 1 |
| Intrathecal cytarabine | 1 |
| Intrathecal methotrexate | 8 and 29 (CNS–) |
| Triple intrathecal therapy | 8, 15, 22 and 29 (CNS1) |
| Block 2 | |
| Cyclophosphamide, 440 mg/m2 IV | 1 to 5 |
| Etoposide, 100 mg/m2 IV | 1 to 5 |
| Methotrexate, 5 g/m2 IV | 22 (pending blood count recovery) |
| Intrathecal methotrexate | 1 and 22 (CNS–) |
| Triple intrathecal therapy | 1 and 22 (CNS1) |
| G-CSF, 5 µg/kg SQ | 6 until ANC .1,500/µl 3 2 days |
| Block 3 | |
| Cytarabine, 3 g/m2 IV every 12 hours | 1, 2, 8 and 9 |
| L-asparaginase, 6,000 U/m2 IM | 2 and 9 at hour 42 after cytarabine |
| G-CSF, 5 µg/kg SQ | 10 until ANC .1,500/µl 3 2 days |

- Abbreviations: IV, intravenous; PO, oral; IM, intramuscular; SQ, subcutaneous; Ph, Philadelphia chromosome; G-CSF, granulocyte colony-stimulating factor; LP, lumbar puncture. Triple intrathecal therapy (methotrexate, cytarabine and hydrocortisone) is continued weekly beyond four doses until two successive lumbar puncture CSF are free of blasts. All intrathecal medications are dosed based on age.

## References:

1. Raetz EA, Borowitz MJ, Devidas M, et al. J Clin Oncol 2008;28:3971–3978.

## Treatment Schedule for ALL Patients with Isolated CNS Relapse:

**Induction (weeks 1–4):**
DEX: 10 mg/m$^2$ orally daily for 28 weeks
Vincristine: 1.5 mg/m$^2$ IV weekly for 4 weeks
Daunomycin: 25 mg/m$^2$ weekly for 3 weeks
TIT: MTX/HC/Ara-C (age-adjusted dose)* IT weekly for 4 weeks

**Consolidation (weeks 5–10):**
Ara-C: 3 g/m$^2$ IV every 12 hours for 4 doses on each of weeks 5 and 8 (a total of 8 doses)
L-asp: 10,000 IU/m2 IM weekly on weeks 5, 6, 8, 9
TIT: MTX/HC/Ara-C (age-adjusted dose) IT week 10

**Intensification 1 (weeks 11–22):**
MTX: 1,000 mg/m$^2$ IV over 24 hours, followed by
MP: 1,000 mg/m$^2$ IV over 8 hours weeks 11, 14, 17 and 20
Etoposide: 300 mg/m$^2$ IV, followed by
CYC: 500 mg/m$^2$ IV weeks 12, 15, 18 and 21
TIT: MTX/HC/Ara-C (age-adjusted dose)* IT weeks 13, 16, 19 and 22

**Reinduction (weeks 23–26):**
DEX: 10 mg/m$^2$ orally daily for 28 days
Vincristine: 1.5 mg/m$^2$ IV weekly for 4 weeks
Daunomycin: 25 mg/m$^2$ IV weekly for 3 weeks

**Intensification 2 (weeks 27–50):**
Ara-C: 3 g/m$^2$ IV every 12 hours for 4 doses in weeks 27, 33, 39, 45
L-asp: 10,000 IU/m$^2$ IM on weeks 27, 28, 33, 34, 39, 40, 45, 46
TIT: MTX/HC/Ara-C (age-adjusted dose)* IT weekly on weeks 30, 36, 42, 48
MTX: 1,000 mg/m$^2$ IV over 24 hours on weeks 31, 37, 43, 49
6MP: 100 mg/m$^2$ IV over 8 hours on weeks 31, 37, 43, 49
Etoposide: 300 mg/m$^2$ IV on weeks 32, 38, 44, 50
CYC: 500 mg/m$^2$ IV on weeks 32, 38, 44, 50

**Irradation (weeks 51–54):**
CR1 < 18 months Craniospinal: 24 Gy cranial and 15 Gy spinal
CR1 ≥ 18 months Cranial 18 Gy ONLY (not spinal)
Dex 10 mg/m$^2$/ orally daily for 21 days
VCR 1.5 mg/m$^2$ IV weekly for 3 weeks 51, 52, 53
L-asp: 10,000 IU/m$^2$ IM x9 on weeks 51–54

**Maintenance (weeks 55–104):**
MP: 75 mg/m$^2$ orally daily342
MTX: 20 mg/m$^2$ IM weekly36
Alternate with
Vincristine: 1.5 mg/m$^2$ IV weekly34
CYC: 300 mg/m$^2$ IV weekly34

Abbreviations: DEX, dexamethasone; VCR, vincristine; DNR, daunomycin; TIT, triple intrathecal therapy; HC, hydrocortisone; Ara-C, Cytarabine; L-asp, L-asparaginase; MP, 6-mercaptopurine; CYC, cyclophosphamide; IV, intravenous, IT, intrathecally; IM, intramuscularly; CR1, first complete remission.

## References:

1. Barredo JC, Devidas M, Lauer SJ, et al. Isolated CNS relapse of Acute Lymphoblastic Leukemia treated with intensive systemic chemotherapy and delayed CNS radiation: a pediatric oncology study. J Clin Oncol 2006; 24:3142–3149.

# 2. ACUTE MYELOID LEUKEMIA

## FAB Classification of AML

Type M0 – acute undifferentiated leukemia

Type M1 – myeloblastic leukemia without maturation; morphologically indistinguishable from L2 morphology

Type M2 – myeloblastic leukemia with differentiation

Type M3 – acute promyelocytic leukemia (APML); most cells abnormal hypergranular promyelocytes; cytoplasm contains multiple Auer rods

Type M3V – microgranular variant of APML; cells with deeply notched nucleus; typical hypergranular promyelocytes less frequent

Type M4 – both myelocytic and monocytic differentiation present in varying proportions

Type M4EOS – associated with prominent proliferation of eosinophils

Type M5 – monocytic leukemia containing poorly differentiated and/or well-differentiated monocytoid cells (the M4 and M5 subtypes are particularly common in children under 2 years of age)

Type M6 – erytholeukemia (Diguglielmo disease)

Type M7 – megakaryoblastic leukemia; associated with myelofibrosis; frequently observed in children with trisomy 21. M7 leukemia has the following characteristics:

- The blast morphology is heterogeneous in appearance, resembling L1 or L2 cells with or without granules and having one to three nucleoli; the cytoplasm has blebs
- Immunophenotype is CD41, CD42, CD61 positive – in addition to CD13 and CD33 positivity
- Electron microscopy demonstrates positive platelet peroxidase (PPO) reaction localized exclusively on the nuclear membrane and the endoplasmic reticulum

## Therapy for Newly Diagnosed AML-protocol

**Course 1 ADE:**

Daunorubicin 50 mg/m2 IV days 1, 3, 5

Cytosine arabinoside 100 mg/m2 IV bolus every 12 hours days 1 to 10 (20 doses)

Etoposide 100 mg/m2 IV 1 hour infusion days 1 to 5

Intrathecal cytarabine age adjusted doses at time of diagnostic LP

**Course 2 ADE:**

Daunorubicin 50 mg/m2 IV daily on days 1, 3, 5

Cytosine arabinoside 100 mg/m2 IV bolus every 12 hours on days 1 to 8 (16 doses)

Etoposide 100 mg/m2 IV daily (1 hour infusion) days 1 to 5

Intrathecal cytarabine age adjusted dosing on day 1

**Course 3 MACE:**

Amsacrinea 100 mg/m2 IV daily (1 hour infusion) days 1 to 5

Cytosine arabinoside 200 mg/m2/d IV (continuous infusion) days 1 to 5

Etoposide 100 mg/m2 IV daily (1 hour infusion) days 1 to 5

Intrathecal cytarabine age adjusted dosing on day 1

**Course 4 MidAC:**

Mitoxantrone 10 mg/m2 IV daily (short infusion) days 1 to 5

Cytosine arabinoside 1.0 gram/m2 12-hourly IV (2 hour infusion) days 1 to 3 (6 doses)

Intrathecal cytarabine age adjusted dosing on day 1

**Course 5 CLASP:**

Cytosine arabinoside 3.0 grams/m2 IV every 12 hours for 4 doses on days 1, 2, 8 and 9

L-asparaginase 6,000 IU/m2 IM days 2 and 9 (3 hours after completion of Ara-c)

## Notes:

All doses are reduced by 25% for children less than 1 year of age.

Age-adjusted intrathecal chemotherapy with cytosine arabinoside: Age 0 to 1 year 20 mg; 1 to 2 years 30 mg; 2 to 3 years 50 mg; 3 year or older 60 mg.

For patients with CNS disease at diagnosis IT therapy with cyatarabine is given twice per week until CSF is clear with two additional doses after clearing of CSF with a minimum of 4 doses of intrathecal therapy.

Abbreviations: LP, lumbar puncture.

## References:

1. Gibson BES, Wheatley K, Hann IM, Stevens RF, Webb D, Hills RK, De Graaf SSN, Harrison CJ. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trails. Leukemia 2005; 19:2130–2138.

# Patients with Refractory or Recurrent Acute Myeloblastic Leukemia

## Reinduction Protocol for Relapsed AML

Cytarabine (Ara-C) 1,000 mg/m2 as a 2 hour infusion every 12 hours for 4 days (8 doses) starting

hour 0 day 0

Mitoxantrone 12 mg/m2 as 1 hour infusion every 24 hours for 4 days beginning day 2 hour 11

Cytarabine (Ara-C) intrathecally on day 0 with age adjusted doses

Decadron eye drops every 4 hours during and for 48 hours after completion of cytosine arabinoside

Granulocyte colony stimulating factor 5 micrograms per kilogram subcutaneously starting 24 hours after last dose of mitoxantrone

## High-dose Ara-C Regimen (The Capizzi Regimen)

Ara-C 3 g/m2 IV over 3 hours every 12 hours for four doses followed by L asparaginase 6,000 units/m2 IM 3 hours after the completion of the fourth dose of Ara-C.

Decadron eye drop every 4 hours beginning before, during and 1 day after the Ara-C treatment

Course 2

Same as Course 1, beginning on day 8. Decadron eyedrops every 4 hours as above

To prevent severe conjunctivitis that can cause pain and photophobia.

Chapter 2

# CHRONIC MYELOID LEUKEMIA (CML)

**WHO Classification of Chronic Myeloproliferative Diseases:**
Chronic myeloid leukemia (Ph chromosome, t (9; 22) (q34; q11), BCR/ABL positive)
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia (and the hypereosinophilic syndrome)
Polycythemia Vera
Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
Essential thrombocythemia
Chronic myeloproliferative disease, unclassifiable

**Treatment of Chronic Phase of CML:**
Imatinib is used as the first line of treatment.

**Dose:**
In children: Chronic phase of CML 340 mg/m2/day orally.

**Frequency of Monitoring Response to Imatinib:**
1. Hematologic: Monitor every 2 weeks until CHR then every 3 months.
2. Cytogenetic: Monitor every 6 months until CCR then annually.
3. Molecular: Monitor every 3 months.

# Chapter 3

# HEMATOLOGY PROTOCOLS

Chapter 3

# ACUTE MYELOID LEUKEMIA

## Induction:

- - Daunorobicin 60-90 mg/m$^2$/day
  Day 1, 2, and 3 during 30 min
- - Ara-C "Cytarabine" 100-200 mg /m$^2$/day continuous infusion on days 1-7

OR

- Daunorubicin 50 mg/m$^2$, I.V. for 5 days
- Cytarabine 100 mg/m$^2$, I.V. (continuous infusion) on days 1-7

## Consolidation:

Courses 1-2-3
Ara- C "Cytarabine" 1.5-3 gm/m$^2$
Twice daily days 1, 3, and 5 given over 3 hours for 3-4 cycles

## Salvage:

- Cytarabine 3000 mg/m$^2$, b.i.d. I.V. (3 hrs infusion) on days 1, 2, 8, and 9
- Mitoxantrone 10 mg/m$^2$, I.V. (30 min infusion), days 3, 4, 10, and 11
- G-CSF, S.C. starting days 12 or 14

## References:


1. National Comprehensive Cancer Network 2012.
2. Fernandez HF et al. Anthracycline dose intensification in acute myeloid leukemia. N. Engl. J. Med. 361 (2009): 1249-1259.
3. Castaigne S et al. Randomized comparison of double induction and timed-sequential induction to a "3+7" induction in adults with AML: long-term analysis of the Acute Leukemia French Association (ALFA) 9000 study. Blood 104 (2004): 2467-2474.
4. Omura GA et al. Treatment of acute myelogenous leukemia: influence of three induction regimens and maintenance with chemotherapy or BCG immunotherapy. Cancer 49 (1982): 1530-1536.
5. Preisler H et al. Comparisonof three remission induction regimens and two postinduction strategies for the treatment of acute nonlymphocytic leukemia: a Cancer and Leukemia Group B study. Blood 69 (1987): 1441-1449.

# ACUTE PROMYELOCYTIC LEUKEMIA

## Induction:

- ATRA 45 mg /$m^2$ p.o in 1-2 divided doses from 1$^{st}$day –"Maximam 90days"
- ARA.C 200mg /$m^2$ I.V. days 3-9 "7 days"
- Daunorobucin 60 mg /$m^2$ I.V. days 3-5

## References:

1. Ades L et al; European APL Group. Very long-term outcome of acute promelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: the European APL Groupexperience. Blood 115 (2010): 1690-1696.
2. Ades L et al. Is cytarabine useful in the treatment oa acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. J. Clin. Oncol. 24 (2006): 5703-5710.
3. Fenaux P et al. Long-term follow-up confirms the benefit of all-trans retinoic acid in acute promyelocytic leukemia. European APL group. Leukemia 14 (200): 1371-1377.

## Consolidation (1): (low dose)

- Daunorobucin 45 mg/$m^2$ I.V. on days 1-2
- ARA-C 100 mg/$m^2$/day continuous infusion on days 1-5

## Consolidation (2): (high dose)

- Daunorobucin 45mg /$m^2$ I.V day 1-3
- ARA-C 1 gr/$m^2$ I.V every 12 hours
- Days 1-4 "8doses"

## Maintenance:

(Note: to be started after end of consolidation for 2 years)

- ATRA 45 mg/$m^2$ P.O. for 15 days quarterly.
- 6 MP "Mercaptopurine" 50 mg/$m^2$/day P.O. daily
- MTX (methotrexate) 15 mg /$m^2$ I.M. once weekly "

## References:


1. Avvisati G et al; GIMEMA, AIEOP, and EORTC Cooperative Groups. AIDA0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood 117 (2011): 4716-4725.
2. Sanz MA et al; PETHEMA and HOVON groups. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood 115 (2010): 5137-5146.
3. Lo-Coco F et al; Italian GIMEMA Cooperative Group. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: resulta of the AIDA-2000 trail of the GIMEMA Group. Blood 116 (20100): 3171-3179.
4. Sanz MA et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood 112 (2008): 3130-3134.
5. Sanz MA et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood 96 (2000): 1247-1253.

# ACUTE LYMPHOBLASTIC LEUKEMIA

## ALL-BFM 95: Protocol I (Branch R)

### 1. Induction:

**Protocol I - Phase I:**

Prednisone 60 mg/$m^2$/ day PO divided into 3 doses on days 1-28
Vincristine 1.5 mg/$m^2$/ day, I.V. on days 8, 15, 22, and 29 (max 2 mg)
Daunorubicin 30 mg/$m^2$/ day IV (1 hr inf) every 24 hrs on days 8, 15, 22, and 29
Asparaginase 10000 IU/ $m^2$/ day IV (1 hr inf) on days 12, 15, 18, 21, 24, 27, 30, and 33
MTX (methotrexate) 12 mg, i.th. on days 1, 15, 29

**Protocol I - Phase II:**

CPM (cyclophosphamide) PI (1h) 1000 mg/$m^2$/ day I.V. on days 36, 64 + Mesna
ARA-C IV (cytarabine) 75 mg/$m^2$/ day, I.V. on days 38-41, 45-48, 52-55, 59-62
6-MP PO (mercaptopurine) (28 d) 60 mg/$m^2$/ day, P.O. on days 36-64
MTX IT (methotrexate) (Dose age adapted: <1 y: 6 mg/ 1y: 8 mg/ 2y: 10 mg/≥ 3y: 12 mg), i.th. on days 45-59

### 2. Consolidation:

**ALL-BFM 95: Protocol M:**

6-MP (mercaptopurine) PO (56 d) 25 mg/$m^2$/ day, P.O. on days 1 (evenings)
HD-MTX PI (methotrexate) 5000 mg/$m^2$, I.V. (24 hrs infusion) on days 8, 22, 36, and 50
Or 12 mg, i.th. On days 8, 22, 36, and 50
LCV (Leucovorin) -Rescue 15 mg/ $m^2$ IV at h 42, 48, and 54
MTX IT (Dose age adapted: <1 y: 6 mg/ 1y: 8 mg/ 2y: 10 mg/≥ 3y: 12 mg)

### 3. Reinduction

**ALL-BFM 95: Protocol II:**

Dexamethasone PO 10 mg/$m^2$/day, on days 1-21
VCR (vincristine) 1.5 mg/$m^2$/day (max 2 mg), I.V. on days 8, 15, 22, and 29
Doxorubicin PI (1h) 30 mg/$m^2$/day, I.V. on days 8, 15, 22, and 29
L-ASP PI (asparaginase) (1h) 10000 IU /$m^2$/day, I.V. on days 8, 11, 15, and 18CPM PI (cyclosporine) (1 h) 1000 mg/$m^2$, I.V. on day 36
ARA-C IV (cytarabine) 75 mg/$m^2$/day, I.V. on days 38,-41, 45-48
6-TG PO (thioguanine) (14 d) 60 mg/$m^2$/day, P.O. on days 36-49
MTX (methotreaxate) (Dose age adapted: <1 y: 6 mg/ 1y: 8 mg/ 2y: 10 mg/≥ 3y: 12 mg), i.th. on days 38, 45

## References:


1. Moricke A et al; German-Austrian-Swiss ALL-BFM Study Group. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 111 (2008): 4477-4489.
2. Nowak-Gottl U et al. Thromboembolic events in children with acyte lymphoblastic leukemia (BFM protocols): prednisone versus dexamethasone administration. Blood 101 (2003): 2529-2533.
3. Schrappe M et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss AALL-BFM Study Group. Blood 95 (2000): 3310+3322.


## 1. Remission Induction:

### a. DVP:

- Daunorubicin 45 mg/m$^2$, I.V. on days 1-3
- Vincristine 2 mg, I.V. on days 1, 8, 15, and 22
- Prednisone 60 mg/m$^2$, P.O. on days 1-35
- * An additional dose of daunorubicin is given on day 14, if bone marrow examination reveals persistent leukemia.

## References:


1. Wiernik PH et al. A randomized trial of induction therapy (daunorubicin, vincristine, pednisone versus daunorubicin, vincristine, prednisone, cytarabine and 6-thioguanine) in adult acute lymphoblastic leukemia with long-term follow-up: an Eastern Cooperative Oncology Group study (E3486). Leuk. Lymphoma 44 (2003): 1515-1521.
2. Vitale A et al. The changing scene of adult acute lymphoblastic leukemia. Curr. Opin. Oncol. 18 (2006): 652-659.
3. Wassman B et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-linetherapy for Philadelphia-possitive acute lymphoblastic leukemia (Ph+ ALL). Blood 108 (2006): 1469-1477.
4. Yanada M, Naoe T. Imatinib combined chemotherapy for Philadelphia chromo-some-possitive acute lymphoblastic leukemia: major chellenges in current practice. Leuk. Lymphoma 47 (20006): 1747-1753.


### b. Induction phase I, weeks 1-4

- Daunorubicin 60 mg/m$^2$, I.V. on days 1, 8, 15, and 22
- Vincristine 1.4 mg/m2, I.V. on days 1, 8, 15, and 22
- Prednisone 60 mg/m$^2$, P.O. on days 1-28
- Asparaginase 10000IU, I.V. or I.M. on days 17-28
- Methotrexate 12.5 mg, I.th. on day 15

## References:

1. Rowe JM et al.; ECOG; MRC/NCRI Adult Leukemia Working Party. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 106 (2005): 3760-3767

## c. Induction phase II, weeks 5-8

- Cyclophosphamide 650 mg/m$^2$, I.V. on days 1, 15, and 29
- Cytarabine 75 mg/m$^2$, I.V. (1 hr infusion) on days 1-4, 11, 15-18, 22-25
- Mercaptopurine 6 mg/m$^2$, P.O. on days 1-28
- Methotrexate 12.5 mg, i.th. on days 1, 8, 15, and 22

## References:

1. Rowe JM et al.; ECOG; MRC/NCRI Adult Leukemia Working Party. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 106 (2005): 3760-3767.

## d. Intensification/CNS prophylaxis (3 cycles):

- Methotrexate* 3000 mg/m$^2$, I.V. on days 1, 8, and 22
- Asparaginase 10000 IU, P.O. on days 2, 9, and 23
- * With standard folinic acid rescue

## References:

1. Rowe JM et al.; ECOG; MRC/NCRI Adult Leukemia Working Party. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 106 (2005): 3760-3767.

# MYELODYSPLASTIC SYNDROME

- Epoetin Beta vials 3000 once- two vial/ week
- Low dose cytarabine S.C.
- Bone Marrow Transplantation

DEFERASIROX tab 250, 500
When S. Ferritin is high in patient who treated with blood transfusion.

## References:

1. National Comprehensive Cancer Network 2012.

# NON-HODGKIN'S LYMPHOMA

## High Stage:

**R-CHOP/ CHOP**

*1st day R= Rituximab 375 mg/m$^2$

** 2nd day cyclophosphamide 750 mg/m$^2$ IV day 1

Adriamycin 50 mg/m$^2$ IV day 1

Vincristine 1.4 mg/m$^2$ (max 2 mg) IV day 1

Prednisone 100 mg/m$^2$ PO day 1-5

A dose of rituximab 375 mg/m$^2$ (I.V.) can be added the day before respective CHOP course.

To be repeated every 3 weeks for 6-8 cycles.

## References:

1. Czuczman MS et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J. Clin. Oncol. 22 (2004): 4711-4716.
2. Hiddemann W et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prdnisone (CHOP) significantly improves the outcome for patients with advanced-stage foolicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German low-Grade Lymphoma Study Group. Blood 106 (2005): 3725-3732.
3. Overman MJ et al. The addition of rituximab to CHOP chemotherapy improves overall and failure-free survival for follicular grade 3 lymphoma. Ann. Oncol. 19 (2008): 553-559.

## Low stage:

**CVP/ R-CVP:**

Cyclophoshamide 750 mg/$m^2$ IV day 1 (1 hour)
Vincristine 1.4 mg/$m^2$ (max 2 mg) I.V. day 1
Prednisone 40 mg/$m^2$ PO day 1-5
A dose of rituximab 375 mg/$m^2$ (I.V.) can be added the day before respective CVP course.
To be repeated every 3 weeks for 8 cycles.
Filgrastim G-CSF 300 mcg S.C.

Given to patients with previous chemotherapy treatments.

## References:

1. Marcus R et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105 (2005): 1417-1423.
2. Marcus R et al. Phase II study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J. Clin. Oncol. 26 (2008): 4579-4586.

# FC / FCR (Fludarabine- Cyclophosphamide- Rituximab) Protocol

## FC Schedule:

- Fludarabine 20 mg/m$^2$ I.V. (30 min inf), day 1-5
- Cyclophosphamide 1000 mg/m$^2$ I.V. (30 min inf), day 1
- To be repeated every 4 weeks.

**OR**

- Fludarabine 25 mg/m$^2$ I.V. (15-30 min inf), day 1-3
- Cyclophosphamide 250 mg/m$^2$ I.V. (15-30 min inf), day 1-3
- To be repeated every 4 weeks.

## FCR Schedule:

- Fludarabine 25 mg/m$^2$ I.V. (15-30 min inf), day 1-3
- Cyclophosphamide 250-300 mg/m$^2$ I.V. day 1-3
- Rituximab 357 mg/m$^2$ I.V. day 1*
- To be repeated every 3 weeks (4 cycles).
- (*) Beginning 2 weeks after the first course of FC and then on day 1 of each cycle.

## References:

1. Sacchi S; Italian Lymphoma Study Group (GISL). Rituximab in combination with fludarabine and cyclophosphamide in the treatment of patients with recurrent follicular lymphoma. Cancer 110 (2007): 121-128.
2. Tam CS et al. Fludarabine, cyclophosphamide, and rituximab for the treatment of patients with chronic lymphocytic leukemia or indolent non-Hodgkin lymphoma. Cancer 106 (2006): 2412-2420.
3. Tam CS et al. Fludarabine and cyclophosphamide using an alternated dose schedule is a highly effective regimen for patients with indolent lymphoid malignancies. Cancer 100 (2004): 2181-2189.

# PEDIATRIC BURKITT'S LYMPHOMA

## Phase I:

Vincristine 1.4 mg/m$^2$ IV day 1 and 36
Cyclophosphamide 500 mg/m$^2$ IV day 1 and 2
Methotrexate 150 mg/ kg IV day 8 (infusions 6h+ chlorambucil)
250 mg/kg IV day 22 (infusions 6h+ chlorambucil)
Etoposide (VB-16) 250 mg/m$^2$ IV day 15
Adriamycin 50 mg/m$^2$ IV day 29
Methotrexate 10 mg/m$^2$ IT week 1, 3, 5
Arac 60 mg/m$^2$ IT week 2, 4, 6

## Phase II:

AraC 1000 mg/m$^2$ IV continous infusions x 4 days 43-46
750 mg/m$^2$ IV days 43, 44, 45, 46
Cisplatin 20- 80 mg/m$^2$ IV continous infusions x 4 days 43- 46
Methotrexate 10 mg/m$^2$ IT week 8

## Phase III:

Ifosfamide 8000 mg/m$^2$ IV day 6, infusion 24 h + Mesna

## CODOX-M Protocol

- Cyclophosphamide 800 mg/m$^2$ I.V. day 1, and 200 mg/m$^2$ I.V. on days 2-5
- Doxorubicin 40 mg/m$^2$ I.V. on day 1
- Vincristine 1.5 mg/m$^2$I.V. on days 1+8 (+15*)
- Methotrexate 1200 mg/m$^2$ I.V. (1 hr infusion) on day 10 then 240 mg/m$^2$ each hr over 23 hrs
- Folinic acid 192 mg/m$^2$ I.V. on day 11 (12 hr after methotrexate), then 12 mg/m$^2$ every 6 hrs (until MTX < $5*10^{-8}$ mol/L)
- Cytarabine 70 mg (**) i.th. on days 1+3
- Methotrexate 12 mg (**) i.th. on day 15

(*) Third dose only in course 3 and only if no neuropathy
(**) For patients > 3 years. Reduced doses in younger patients.

## References:

1. National Comprehensive Cancer Network 2012.
2. Adde M et al. Additional chemotherapy agents improve treatment outcome for children and adults with advanced B-cell lymphomas. Semin. Oncol. 25 (Suppl 4) (1998): 33-39; discussion 45-48.
3. Lacasce A et al. Modified Magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk. Lymphoma 45 (2004): 761-767.
4. Mead GM et al; UK National Cancer Research Institute Lymphoma Clinical Studies Group; Australian Leukemia and Lymphoma Group. A prospective clinicopathologic study of dose-modified CODOX-M/VAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY 10 trial). Blood 112 (2008): 2248-2260.

# RESISTENT LYMPHOMA (HODGKIN'S & NON-HODGKINS)

**ICE chemotherapy:**
Ifosfamide 5 mg/m$^2$ day 2 + mesna
Carboplatin day 2
Etoposide days 1, 2, 3
G-CSF support
Hydration before therapy

# Chronic Lymphotic Leukemia

**Chlorambucil +/- Prednisone Protocol**
**Chlorambucil schedule:**

- Chlorambucil 40 mg/m$^2$ P.O. day 1

Or

- Chlorambucil 10 mg/m$^2$ P.O. day 1-7

Or

- Chlorambucil 0.4 mg/kg (starting dose) P.O. day 1*
- To be repeated every 4 weeks
- (*) to be repeated every 2 weeks (max 24 cycles) with a dose increase by 0.1 mg/kg at each treatment course up to 0.8 mg/kg in case treatment was well tolerated.

The combinations of chlorambucil + prednisone dose not appear to result in generally superior survival when compared to chlorambucil alone. It may be preferable, however, in patients with autoimmune phenomena (e.g. autoimmune hemolytic anemia or thrombocytopenia) associated with CLL.

**Chlorambucil + prednisone schedule:**

- Chorambucil 5 mg/m$^2$ P.O. day 1-3
- Prednisone 75 mg P.O. day1
- Prednisone 50 mg P.O. day 2
- Prednisone 25 mg P.O. day 3
- The chlorambucil is to be raised by 0.1 mg/kg until the patient resonds or develops toxic effects. To be repeated every 2 weeks.

## References:

1. Catovsky D et al; UK National Cancer Research Institute (NCRI) Haematological Oncology Clinical Studies Group. NCRI Chronic Lymphocytic Leukaemia Working Group. Assessment of fludarabine plus cyclophsphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomized controlled trial. Lancet 370 (2007): 230-239.
2. Eichohhorst BF et al; German CLL Study Group (GCLLSG). First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 114 (2009): 3382-3391.

## Anti-CD 20 monoclonal antibodies

### 1. Rituximab:

- Rituximab 375 mg/m$^2$, I.V. weekly *4

Rituximab can be successfully combined with chemotherapy

Dose escalation (achieved by a thrice-weekly dosing schedule) improves results in previously treated patients. Addition of fresh frozen plasma of fludarabine refractory CLL patients).

### References:

1. Hainsworth JD et al. Single agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. J. Clin. Oncol. 21 (2003): 1746-1751.
2. Itala M et al. Standard-dose anti-CD20 antibody rituximab has efficacy in chronic lymphocytic leukemia: results from a Nordic multicentre study. Eur. J. Haematol. 69 (2002): 129-134.

### 1. FCR

- Fludarabine 25-30 mg/m$^2$, I.V. on days 1-3
- Cyclophosphamide 250-300 mg/m$^2$, I.V. on days 1-3
- Rituximab 375-500 mg/m$^2$, I.V. on day 1

### References:

Tam CS et al. Pentostatn, cyclophosphamide, and rituximab regimen in older patients with chronic lymphocytic leukemia. Cancer 109 (2007): 2291-2298.

### High Stage (1):

(1) R-CHOP

1$^{st}$ day – Rituximab 375 mg/m$^2$ day 1.

2$^{nd}$ day CHOP

(2) Rituximab 375 mg/m$^2$ day1.

Fludarabin + Cydophosphamide X5 days

### Low stage:

- Mitoxantrone 10 mg/m$^2$ I.V – I $^{st}$ day
- Chlorambucil 10mg /m$^2$ P.O day 2-7
- Prednisone 60mg/m$^2$ P.O day 2-7

Filgrastim 300 Mcg

Given to patients with previous chemotherapy treatments.

# HAIRY CELL LEUKEMIA

## Interferon alpha:

- Various dosage regimens can be used
- Interferon 0.5-1.0 * $10^6$ IU, s.c. daily or 3/week

Or

- Interferon 3.0 * $10^6$ IU, s.c. daily or 3/week

Response evaluation after 2-3 months, continuation of treatment in responders (6-12 months overall). May be appropriate if a patient is severly cytopenic.

In responders, dose can be scaled down to once weekly and continued long term.

## References:

1. National Comprehensive Cancer Network 2012.
2. Damasio EE et al. Alpha-interferon as induction and maintenance therapy in hairy cell leukemia: a long-trm follow-up analysis. Eur. J. Haematol. 64. (2000): 47-52.
3. Ramakrishna R, Manoharan A. Sustained long-term remissions with weekly interferon maintenance therapy in hairy cell leukemia. Asia Pac. J. Clin. Oncol. 6 (2010): 210-212.

Chapter 3

# HODGKIN'S DISEASE

**ABVD (First-line)**

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1, 15 | Doxorubicin | 25 | 0.9 % NaCl | 250 | 1 hr | IV |
| 1, 15 | Bleomycin | 5-10 | 0.9% NaCl | ------ | Bolus | IV |
| 1, 15 | Vinblastine | 6 | ----- | ------ | Bolus | IV |
| 1, 15 | Dacarbazine | 375 (or 250) | 0.9 % NaCl | 500 | 30 mins | IV |
| Repeat cycle every 28 days for 6 cycles.<br>Caution: cardiac toxicity of Doxorubicin at cumulative doses ≥ 500 mg/m$^2$. | | | | | | |

## References:


1. National Comprehensive Cancer Network 2012.
2. Anselmo AP et al. Intermediate stage Hodgkin's disease: preliminary results on 210 patients treated with four ABVD chemotherapy cycles plus extended versus involved field radiotherapy. Anticancer Res. 24 (2004): 4045-4050.
3. Duggan BD et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J. Clin. Oncol. 21 (2003): 607-614.
4. Eich HT et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD 11 trial. J. Clin. Oncol. 28 (2010): 4199-4206.

**MOPP:**

## MOPP protocol

- Nitrogen mustard: 6mg/$m^2$ IV on days 1 and 8
- Vincristine: 1.4 mg/$m^2$ IV on days 1 and 8
- Procarbazine*: 100 mg/$m^2$ PO on days 1-14
- Prednisone: 40 mg/$m^2$ PO on days 1-14

Repeat cycle every 28 days.

Filgrastim 300mcg after chemotherapy

## MOPP/ ABV hybrid regimen:

- Nitrogen mustard 6 mg/$m^2$ I.V. day 1
- Vincristine 1.4 mg/$m^2$ (max 2 mg) I.V. day 1
- Procarbazine 100 mg/$m^2$ P.O. day 1-7
- Prednisone 40 mg/$m^2$ P.O. day 1-14
- Doxorubicin 35 mg/$m^2$ I.V. day 8
- Bleomycin 10 mg/$m^2$ I.V. day 8
- Vinblastine 6 mg/$m^2$ I.V. day 8
- To be repeated every 4 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Ferme C et al; EORTC-GELA H8 Trial. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N. Engl. J. Med. 357 (2007): 1916-1927.

## COPP-ABVD alternating regimen:

- Cyclophosphamide 650 mg/m$^2$ I.V. day 1+8
- Vincristine 1.4 mg/m$^2$ (max 2 mg) I.V. day 1+8
- Procarbazine 100 mg/m$^2$ P.O. day 1-14
- Prednisone 40 mg/m$^2$ P.O. day 1-14
- Doxorubicin 25 mg/m$^2$ I.V. day 29+43
- Bleomycin 10 mg/m$^2$ I.V. day 29+43
- Vinblastine 6 mg/m$^2$ I.V. day 29+43
- Dacarbazine 375 mg/m$^2$ I.V> day 29+43
- To be repeated every 8 weeks.

## References:

1. National Comprehensive Cancer Network 2012.
2. Diehl V et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N. Engl. J. Med. 348 (2003): 2386-2395.

## Stanford V Protocol

- Nitrogen mustard: 6mg/$m^2$ IV on day 1
- Doxorubicin: 25 mg/$m^2$ Iv on days 1 and 15
- Vinblastine: 6 mg/$m^2$ IV on days 1 and 15
- Vincristine: 1.4 mg/$m^2$ IV on days 8 and 22
- Bleomycin: 5 U/$m^2$ IV on days 8 and 22
- Etoposide: 60 mg/$m^2$ IV on days 15 and 16
- Prednisone: 40 mg PO every other day

Repeat cycle every 28 days.

In patients > 50 years of age, vinblastine dose reduced to 4 mg/$m^2$ and vincristine dose reduced to 1 mg/$m^2$ on weeks 9 and 12. Dose of prednisone tapered starting on week 10. Prophylactic Bactrim DS PO bid and acyclovir 200 mg PO t.i.d.

## References:

1. National Comprehensive Cancer Network 2012.
2. Abuzetun JY et al; Nebraska lymphoma Study Group. The Stanford V regimen is effective in patients with good risk Hodgkin lymphoma but radiotherapy is a necessary component. Br. J. Haematol. 144 (2009): 531-537.
3. Horning SJ et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J. Clin. Oncol. 20 (2002): 630-637.

## BEACOPP Protocol (intensified)

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Cyclophosphamide | 1250 | 0.9 % NaCl | 500 | 1 hr | I.V. |
| 1 | Doxorubicin | 25-35* | 0.9 % NaCl | 250 | 1 hr | I.V. |
| 1-3 | Etoposide | 100-200* | 0.9 % NaCl | 1000 | 1 hr | I.V. |
| 1-7 | Procarbazine | 100 | ----- | ----- | ------ | P.O. |
| 1-14 | Prednisone | 40 | ----- | ----- | ----- | P.O. |
| 8 | Vincristine | 1.4 (*) | 0.9 % NaCl | 100 | 10 minutes | I.V. |
| 8 | Bleomycin | 10 | ----- | ----- | Bolus | I.V. |
| Repeat every 22 days.<br>* Increased-dose (escalated) regimen with G-CSF support | | | | | | |

**Notes:**

- Caution: cardiac toxicity of doxorubicin at cumulative doses ≥500 mg/m$^2$.
- Etoposide should be dissolved in 1000 ml 0.9% NaCl if total dose is ≥200 mg.
- (*): Vincristine max. 2 mg.
- Mesna: 250 mg/m$^2$ in 500 ml 0.9% NaCl over 30 minutes immediately before administration of cyclophosphamide, thereafter 1250 mg/m$^2$ over 12 hr (start of cyclophosphamide administration).
- G-CSF obligatory on day 8 until leukocytes >1000 /mm$^3$ is achieved and the nadir is crossed. Continuation of therapy only 48 hrs after discontinuation of G-CSF.

Dose: 300 mcg/d s.c. if bodyweight <75 kg, 450 mcg/kg s.c. if bodyweight >75 kg.

## References:


1. National Comprehensive Cancer Network 2012.
2. Avigdor A et al. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT is an effective regimen for advanced high-risk Hodgkin's lymphoma. Ann. Oncol. 21 (2010): 126-132.
3. Diehl V et al. BEACOOP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. J. Clin. Oncol. 16 (1998): 3810-3821.
4. Federico M et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patienst with advanced Hodgkin's lymphoma: results from the HD2000 Grippo Italiano per Studio dei Linformi. Trial. Clin. Oncol. 27 (2009): 805-811.

## BEACOPP Basis Protocol

| D | Drug | Do, mg/m$^2$ | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1 | Cyclophosphamide | 650 | 0.9 % NaCl | 500 | 1 hr | I.V. |
| 1 | Doxorubicin | 25 | 0.9 % NaCl | 250 | 30minutes | I.V. |
| 1-3 | Etoposide | 100 | 0.9 % NaCl | 100 | 10 minutes | I.V. |
| 1-7 | Procarbazine | 100 | ----- | ----- | ----- | P.O. |
| 1-14 | Prednisone | 40 | ----- | ----- | ----- | P.O. |
| 8 | Vincristine | 1.4 (*) | 0.9 % NaCl | 100 | 10 minutes | I.V. |
| 8 | Bleomycin | 10 | ----- | ----- | Bolus | I.V. |
| Repeat every 29 days for 8 cycles. | | | | | | |

**Notes:**

- Caution: cardiac toxicity of doxorubicin at cumulative doses ≥ 450 or 500 mg/m$^2$.
- Etoposide should be dissolved in 100 ml 0.9% NaCl if total dose is ≥200 mg.
- (*): Vincristine max. 2 mg.
- Mesna: 130 mg/m$^2$ in 500 ml 0.9% NaCl over 30 minutes immediately before administration of cyclophosphamide, thereafter 650 mg/m$^2$ over 12 hr (start of cyclophosphamide administration).

## References:

1. National Comprehensive Cancer Network 2012.
2. Avigdor A et al. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT is an effective regimen for advanced high-risk Hodgkin's lymphoma. Ann. Oncol. 21 (2010): 126-132.
3. Diehl V et al. BEACOOP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. J. Clin. Oncol. 16 (1998): 3810-3821.
4. Federico M et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patienst with advanced Hodgkin's lymphoma: results from the HD2000 Grippo Italiano per Studio dei Linformi. Trial. Clin. Oncol. 27 (2009): 805-811.

# CHRONIC MYELOID LEUKEMIA

- Imatinib tab 100, 400 mg, 400-600mg/P.O/ day

## Imatinib Protocol

| D | Drug | Do, mg | Di | V, ml | T | R |
|---|---|---|---|---|---|---|
| 1-* | Imatinib mesylate | 400 | ------- | ------ | ------ | P.O. |
| Continuous administration<br>In CML patients in an accelerated phase, the initial dose is 600 mg daily.<br>Tratment should be continued as lon as the patients has benefit. | | | | | | |

**Note:**

- For special cases:
- Pregnancy: Hydroxyurea tab. 500 mg

## References:


1. National Comprehensive Cancer Network 2012.
2. Baccarani M et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European Leukemia Net Study. Blood 113 (2009): 4497-4504.
3. Cortes JE et al. High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: high rates of rapid cytogenetic and molecular responses. J. Clin. Oncol. 27 (2009): 4754-4759.
4. Hehlmann R et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-α in newly diagnosed chronic myeloid leukemia. J. Clin. Oncol. 29 (2011): 1634-1642.

# MULTIPLE MYELOMA

## High-dose dexamethasone

- Dexamethasone 40 mg/d P.O. on days 1-4, 9-12, 17-20
- To be repeated every 4-5 weeks.

## References:

1. 1. Alexanian R et al. High-dose glucocorticoid treatment of resistant myeloma. Ann. Intern. Med. 105 (1986): 8-11.

## Conventional induction and maintenance therapy Melphalan + Prednisolone/prednisone (MP) Protocol*

**Melphalan + Prednisolone/prednisone Schedule:**

- Melphalan* 15 mg/$m^2$ I.V. (short inf) day 1
- Prednisolone 40-60 mg/$m^2$ P.O. day 1-4
- To be repeated every 4 weeks.
- (*) Daily dosage can be increased in following cycles, if leucocytes >3,000/$mm^3$ and thrombocytes >100,000/$mm^3$.

**OR**

- Melphalan 0.25 mg/kg P.O. day 1-4
- Prednisone 100 mg P.O. day 1-4
- To be repeated every 6 weeks (until plateau phase).

## References:

1. National Comprehensive Cancer Network 2012.
2. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. J. Clin. Oncol. 16 (1998): 3832-3842.
3. Waage A et al; Nordic Myeloma Study Group. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 116 (2010): 1405-1412.

## Cyclophosphamide + Dexamethasone Protocol:

- Cyclophosphamide 1000 mg/m$^2$ I.V> (1 hr inf) day 1
- Dexamethasone 40 mg/d P.O. day 1-4, 9-12
- To be repeated every 3 weeks, max 3 cycles.

## References:

1. Mellqvist U-H et al; for the Nordic Myeloma Study Group. Cyclophosphamide plus dexamethasone is an efficient initial treatment before high-dose melphalan and autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of a randomized comparison with vincristine, doxorubicin, and dexamethasone. Cancer 112 (2008): 129-135.

### $M_2$ Protocol:

- Cyclophosphamide 650 mg I.V /$m^2$ day 1
- Vincristin 2 mg I.V day 1
- Melphalan 4 mg/$m^2$ day 1-7
- Prednisone 40 mg/$m^2$ day 1-7

Repeat every 28 days

### Bisphosphonate:

- Pamidronic acid I.V every 2-3 weeks.

Before chemotherapy:
Granisetron vail 3 mg and tab. 1mg
For nausea and vomiting

After chemotherapy
Filgrastim 300 Mcg S.C

# THALASEMIA

Thalasemia Major and intermedia with high ferritin and iron over load:

Deferasirox Tab. 250, 500.

30-40 mg/kg /day