General introduction to the concepts of chemotherapy
NVvO Basiscursus Oncologie
5 maart 2015

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Chemotherapy: targeting proliferation in cancer

Proliferation

Mitosis

Anti metabolites

DNA damaging agents

Spindle damaging agents

DNA damage

Check point 1

Spindle damage

Check point 2

5FU
Gemcitabine
Ara-C
MTX

platinum
Topoisomerase I/II inh alkylators
Mitomycin C

Taxanes
Vinca alkaloids
Vinorelbine
Mechanism of 5-FU anti-metabolite action

5-FU \rightarrow 5-FUR \rightarrow 5-FUdR

5-FU \rightarrow 5-FdUMP

5-FdUMP \rightarrow 5-FdUTP \rightarrow \text{Incorporation into DNA}

Uridine phosphorylase

Thymidine phosphorylase

Thymidine kinase

Phospho-Ribosyl-transferase

Uridine kinase

Inhibition of TS

\text{Incorporation into RNA}

\text{Cellular thymidine depletion}

+ reduced folate
Chemotherapy: targeting proliferation in cancer

**Proliferation**
- Growth and preparation for mitosis
- DNA replication
- Growth and normal metabolic roles

**Interphase**
- G₀
- G₁
- S

**Mitotic phase**
- Prophase
- Metaphase
- Anaphase
- Telophase

**First growth phase**
- G₂

**Mitosis**
- DNA damage
- Checkpoint 1
- Spindle damage
- Checkpoint 2
- DNA damaging agents
- Spindle damaging agents

**Anti metabolites**
- 5FU
- Gemcitabine
- Ara-C
- MTX

**DNA damaging agents**
- platinum
- Topoisomerase I/II inh
- alkylators
- Mitomycin C

**Spindle damaging agents**
- Taxanes
- Vinca alkaloids
- Vinorelbine
Mechanism of DNA damaging agents

**Double strand breaks**
- Topoisomerase inh
- Platinum
- Alkylators

**Single strand breaks**
- Platinum

**Crosslinks**
- Platinum
- Alkylators

**Cell cycle arrest and repair**
**Cell cycle progression and death due to DNA damage**
**Cell cycle arrest and apoptosis**
Chemotherapy: targeting proliferation in cancer

Proliferation
- Mitotic phase
- Metaphase
- Anaphase
- Telophase
- Interphase
- Growth and preparation for mitosis
- Growth and normal metabolic roles
- DNA replication

Anti metabolites
- 5FU
- Gemcitabine
- Ara-C
- MTX

Mitosis
- DNA damage
- Check point 1
- Spindle damage
- Check point 2

DNA damaging agents
- platinum
- Topoisomerase I/II inh
- alkylators
- Mitomycin C

Spindle damaging agents
- Taxanes
- Vinca alkaloids
- Vinorelbine
Mechanisms of mitotic spindle poisons

Normal division

Abnormal cell divisions
Chromosome instability

Partial Checkpoint

- Single Chromosome Loss
  - Cancer

Inactive Checkpoint

- Massive Chromosome Loss
  - Death

Strategies to exploit checkpoint weakness in cancer cells:

Stress the checkpoint: taxanes

Block the checkpoint: new agents such as Aurora inh
Side effects chemotherapy: on target toxicity

Other on target toxicities are: diarrhea/ bone marrow suppression
On target toxicities can be treated (GCSF/Palifermin/coldcap/loperamide etc)
Side effects chemotherapy: off target toxicity

Vestibulaire centra
- Hist
- AC

Chemoreceptor trigger zone (hersenstam)
- NK1
- D2
- 5HT3

Mechano- en chemoreceptoren (viscera, peritoneum)
- AC
- Hist
- D2
- 5HT3

Hogere centra

Braakcentrum (hersenstam)
- Hist
- AC
- 5HT3
- NK1

Nervus vagus
- AC
- D2
- 5HT3
### Differences between chemotherapeutic agents

<table>
<thead>
<tr>
<th>Hoog (90% braken)</th>
<th>Intermediair (31-90%)</th>
<th>Laag (10-30%)</th>
<th>Minimaal (&lt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatinum</td>
<td>Carboplatin</td>
<td>Paclitaxel</td>
<td>Bleomycine</td>
</tr>
<tr>
<td>DTIC</td>
<td>Oxaliplatin</td>
<td>Docetaxel</td>
<td>Vinca-alkaloiden</td>
</tr>
<tr>
<td>Cyclofosfamide (hoge doses)</td>
<td>Cyclofosfamide</td>
<td>Mitoxantrone</td>
<td>Fludarabine</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>Etoposide</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Mitoxine</td>
<td>Anthracyclines</td>
<td>Methotrexaat</td>
<td>Chloorambucil</td>
</tr>
<tr>
<td>Streptozotocine</td>
<td>Irinotecan</td>
<td>Gemcitabine</td>
<td>Hydroxy-urea</td>
</tr>
<tr>
<td>Carmustine</td>
<td>Ara-C (hoge doses)</td>
<td>Ara-C</td>
<td>6-Thioguanine</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Temozolomide</td>
<td>5-Flurouracil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capecitabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitomycine</td>
<td></td>
</tr>
</tbody>
</table>

*Off Target toxicity is substance dependent, but may be class common!*
What are the costs of chemotherapy for the patient

- Hematologic toxicity: on target side effect (proliferation)
- Non-hematologic toxicity:
  - Nausea/vomiting: direct effect areas in the brain that govern emesis
  - Mucosal toxicity (mouth/GI tract): on target side effect (proliferation)
  - Hair loss: on target side effect (proliferation)
  - Fatigue
- Various other toxicities that are drug specific:
  - Neurotoxicity
  - Skin toxicity
  - Hepato/renal/lung toxicity

*Chemotherapy induces considerable side effects and affect quality of life*
Conclusions on chemotherapy

- Chemotherapy targets the first and most important hallmark of cancer: proliferation

- Different targets are used throughout the cell cycle: a process that has been well-characterized

- Chemotherapy comes at the price of considerable side effects
How do we use chemotherapy?

- Curative
- Adjuvant
- Induction/ neo-adjuvant
- Palliative
Curative chemotherapy

- Germ cell tumors
- Persistent trophoblast tumors
- Small cell sarcomas/ small cell carcinomas
Survival of patients with metastatic GCC before and after the introduction of cisplatin.
Metastatic Germ Cell Cancer

< 1975  Vinblastine (V)
        Bleomycin (B)

1975 - 1985  Cisplatin (P) V B   (PVB)

1985 - 2001  B Etoposide (E) P   (BEP)

BEP:
- Superior to PVB
- Less toxic than PVB

→ BEP became gold standard chemotherapy regimen.

Williams, 1987
Germ Cell Cancer
IGCCCG Consensus Classification

Good prognosis
- 60% all patients
- 90% PFS
- NS + S
- Low markers
- No non-pulmonary visceral mets

Intermediate prognosis
- 25% all patients
- 75% PFS
- NS
- Intermediate markers
- AFP $\geq$ 1000-10,000 ng/ml
- HCG $\geq$ 5000-50,000 U/l
- LDH 1.5-10 x ULN
- S
- Non-pulmonary visceral mets

Poor prognosis
- 15% all patients
- < 50% PFS
- NS
- High markers and/or
- Non-pulmonary visceral mets

JCO, 1997
Metastatic Germ Cell Cancer

Upfront chemotherapy

good prognosis disease → decrease the toxicity of 4 BEP cycles

intermediate/poor prognosis disease → improve the results

De Wit, Semin Surg Oncol 1999
Optimal chemotherapy in good prognosis GCC

Decrease toxicity, while maintaining efficacy

- delete bleomycin
- substitute carboplatin for cisplatin
- decrease number of cycles
Optimal chemotherapy in good prognosis

 GCC

Delete bleomycin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR</th>
<th>OS</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 PVB</td>
<td>94%</td>
<td>95%</td>
<td>“non bulky”</td>
</tr>
<tr>
<td>(n=222)</td>
<td></td>
<td>NS</td>
<td>“non-visceral”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.02</td>
</tr>
<tr>
<td>4 PV</td>
<td>89%</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>3 BEP</td>
<td>94%</td>
<td>86%</td>
<td>“favorable”</td>
</tr>
<tr>
<td>(n=171)</td>
<td></td>
<td>NS</td>
<td>Indiana</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.01</td>
</tr>
<tr>
<td>3 EP</td>
<td>88%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>4 BE_{360}</td>
<td>95%</td>
<td>93%</td>
<td>“ultra good”</td>
</tr>
<tr>
<td>P</td>
<td>p = 0.007</td>
<td>NS</td>
<td>EORTC</td>
</tr>
<tr>
<td>(n=419)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 E_{360}P</td>
<td>87%</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

Optimal chemotherapy in good prognosis GCC

Delete bleomycin

→ bleomycin is essential component in:

4 PVB  Levi JCO 1993
3 BEP  Loehrer JCO 1995
4 \(BE_{360}^P\)  De Wit JCO 1997

none of these regimens can be considered standard treatment
Optimal chemotherapy in good prognosis GCC

Reduce number of cycles

<table>
<thead>
<tr>
<th></th>
<th>CR(NED)</th>
<th>PFS</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>98%</td>
<td>92%</td>
<td>“favorable”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Indiana</td>
</tr>
<tr>
<td>4 BEP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=184)</td>
<td>&lt; 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 BEP</td>
<td>97%</td>
<td>92%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PFS</th>
<th>IGCCCG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 BEP-1 EP</td>
<td>75%</td>
<td>89%</td>
<td>&lt; 5%</td>
<td>good</td>
</tr>
<tr>
<td>(n=812)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 BEP</td>
<td>73%</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Einhorn, JCO 1989, 2) De Wit, JCO 2001
### EORTC/MRC study of 3 BEP vs 3 BEP-1 EP.

3 vs 4 cycles (3 BEP vs 3 BEP-1EP). 5 day schedule vs 3 days per cycle.

<table>
<thead>
<tr>
<th>3 BEP</th>
<th>3 BEP-1 EP</th>
<th>2 x 2 factorial design equivalence study assuming a 2 y PFS 92% difference &lt; 5%, power 90%, significance level 10% (1-sided), 774 patients needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>3 days</td>
<td>3 days</td>
<td></td>
</tr>
</tbody>
</table>
Progression-Free Survival (Intent to treat)
Comparison of the number of cycles

PFS at 2 years
- 3 BEP: 90.35%
- 3 BEP-1 EP: 89.35%

Difference in PFS:
- 0.99 (80% CI: -3.81 to +1.83)

Hazard Ratio:
- 0.934 (80% CI: 0.71 - 1.24)

Number of patients at risk:

<table>
<thead>
<tr>
<th>Year</th>
<th>3 BEP</th>
<th>3 BEP-1 EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>1</td>
<td>406</td>
<td>406</td>
</tr>
<tr>
<td>2</td>
<td>352</td>
<td>344</td>
</tr>
<tr>
<td>3</td>
<td>219</td>
<td>204</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>
Progression-Free Survival (Intent to treat) Comparison of the number of days

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>339</td>
<td>290</td>
<td>175</td>
<td>66</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>342</td>
<td>296</td>
<td>186</td>
<td>55</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

PFS at 2 years 3 days: 89.67%
PFS at 2 years 5 days: 88.75%

Difference in PFS: 0.92% (80% CI: -4.08 to +2.24)

Hazard Ratio: 1.05 (80% CI: 0.78 - 1.41)
Comparison of the number of cycles:

Difference in PFS at 2 years
- 0.99 (80% CI: -3.81 to + 1.83)

Equivalence is claimed for both comparisons as the upper bound of the 80% CI is < 5%

Comparison of the number of days:

Difference in PFS at 2 years
- 0.92 (80% CI: -4.08 to + 2.24)

EORTC/MRC study of 3 BEP vs 3 BEP-1 EP. Conclusions

I 3 cycles of BEP is sufficient therapy in good prognosis germ cell cancer

II administration of the chemotherapy in 3 days has no detrimental effect on the effectiveness of the BEP regimen.
Optimal chemotherapy in good prognosis GCC

- delete bleomycin / reduce number of cycles
- etoposide-cisplatin based chemotherapy

3 EP inferior
4 E\textsubscript{360}P inferior
3 BEP equivalent to 4 cycles good risk IGCCCG

→ 3 BEP standard treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS</th>
<th>Good risk IGCCCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 BEP</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>3 BEP-1EP</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>4 EP (Memorial)*</td>
<td>92%</td>
<td>good IGCCCG (n = 289)</td>
</tr>
</tbody>
</table>

→ 4 EP alternative treatment option if no bleomycin is given

* Kondagunta, JCO 2005
## Optimal chemotherapy in good prognosis GCC

<table>
<thead>
<tr>
<th></th>
<th>CR/PRm-1999*</th>
<th>EFS 2 y 1999*</th>
<th>EFS 4 y 2003*</th>
<th>PFS 4 y 2003</th>
<th>EFS 4 y IGCCCG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 208</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3 BEP</strong></td>
<td>93%</td>
<td>86% (15)</td>
<td>88% (28)</td>
<td>89% (15)</td>
<td>90%</td>
</tr>
<tr>
<td><strong>4 EP</strong></td>
<td>91%</td>
<td>82% (19)</td>
<td>84% (14)</td>
<td>82% (23)</td>
<td>84%</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>NS (0.6)</td>
<td>NS (0.3)</td>
<td>NS (0.08)</td>
<td>NS (0.06)</td>
<td>(0.05)</td>
</tr>
</tbody>
</table>

* Culin, ASCO 1999, Culin, ASCO
Optimal chemotherapy in good prognosis GCC

Primary hypothesis: equivalence <10% diff (90 to 80)
- 5% equivalence study needs 800 patients

Different 0 hypothesis: detect a difference of 10%
- needs 61 events
- needs 408 patients

N = 257 is underpowered for either comparison

Culine, ASCO 2005
Impact of the Treating Institution on OS
(BOP/VIP vs BEP-EP, N = 380)

<5 pts vs. ≥5 pts: HR 1.85 (1.16-3.03), P < 0.01

Collette et al, JNCI 1999
## Impact of the Treating Institution on OS

### dose adherence/ surgery/ cause of death

<table>
<thead>
<tr>
<th></th>
<th>&lt; 5 patients (n = 55)</th>
<th>≥ 5 patients (n = 325)</th>
<th>2-sided P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative dose Intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>95%</td>
<td>98%</td>
<td>&gt; 0.01</td>
</tr>
<tr>
<td>Etoposide</td>
<td>90%</td>
<td>95%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Surgery, if residual masses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (52%)</td>
<td>232 (65%)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant disease</td>
<td>15 (27%)</td>
<td>53 (16%)</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>7 (13%)</td>
<td>20 (6%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Collette et al, JNCI 1999
Adjuvant chemotherapy

- Breast cancer
- Colorectal cancer
- Pancreatic cancer
- Lung cancer
- GBM
Chemotherapy effect: can we cure patients?

Chemotherapy increases cure rate in primary treatment setting

Lancet 2005: 365; 1687
En als je dan klaar bent: wat dan?

Te behandelen patienten

| 50% | 50% |

Behandelde patienten

| 50% | 10% | 40% |

We behandelen tussen de 8-10 mensen met chemotherapie om 1 leven te redden!

Er is geen onderscheid te maken wie in welke groep zit, ook niet achteraf.
Improving selection may be a way to limit harm and maximize benefit.

A. All Patients

Probability of Remaining Metastasis-free

No. at Risk

Good signature

Years

0 2 4 6 8 10 12

P<0.001

B. All Patients

Overall Survival

No. at Risk

Good signature

Years

0 2 4 6 8 10 12

P<0.001

E. Lymph-Node–Positive Patients

Probability of Remaining Metastasis-free

No. at Risk

Good signature

Years

0 2 4 6 8 10 12

P<0.001

F. Lymph-Node–Positive Patients

Overall Survival

No. at Risk

Good signature

Years

0 2 4 6 8 10 12

P<0.001
Induction chemotherapy

Maybe we can help surgeons to cure more patients?
The basic idea:

Localized cancer: too big to perform surgery

Chemotherapy for downsizing

Secondary resection

Cure
Efficacy of induction

Unresectable liver metastases: 20–25% long-term survival after induction chemotherapy and resection

Problems

- Induction chemotherapy needs response: more chemo often gives more response.... And more toxicity

- Response is no always concentric..... To cure you need to resect/irradiate original tumor volume

- Resectability is a subjective criterion.. Studies never realized homogenous inclusion

- NNT vary from 4-10....
Palliative chemotherapy
Chemotherapy shrinks tumors and increases survival time: if tumors are sensitive
Gain of palliative chemotherapy

- Breast cancer: median survival from 6 months to >3 years
- Colorectal cancer: median survival from 6 months to 2-3 years
- Lung cancer: disappointing results median survival up to 9 months
- Prostate cancer: median survival to >2 years
- Pancreatic cancer first advances: up to 1 year overall survival
- Etc....
Conclusions

- Chemotherapy cures a number of cancers
- Adjuvant chemotherapy helps to cure common cancers, however remains “blind”
- Palliative chemotherapy increases overall survival in many disease types