Management of relapsed testicular cancer

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Conflict of interest

- Travel support: Amgen, Merck, MSD, Servier
- Advisory board: MSD, Amgen
- Honoraria: MSD, Merck, Pierre-Fabre
Most patients with metastatic germ-cell tumors will be cured by three to four cycles of BEP.

Except some...
Background

- **first-salvage treatment**
  
  favorable responses 60-80%
  
  long term survival 30-70%

- **second or subsequent salvage treatment**
  
  favorable responses 30%-40%
  
  long-term survival 15-25%
Case

- 24 year old, right-sided gonadal non-seminoma
  (40% chorio, 30% embryonal, 10% yolk-sac, 10% seminoma, 10% teratoma)
- enlarged abdominal lymphnodes, few pulmonary metastases
- markers: HCG 37.401 U/l, AFP 432 ng/ml, LDH 432 U/l pre orch
  markers: HCG 2.927 U/l, AFP 60 ng/ml, LDH 377 U/l post orch
- treatment with BEP x 3, CR with chemo alone
- check at 6 months, symptomatic with dyspnea
  => lung, liver, spleen, kidney, multiple brain metastases
  => HCG 4.606 U/l, AFP 3.1 ng/ml, LDH 702 U/l
Learning Objectives

- first-salvage treatment
- second and subsequent salvage treatment
- late relapse
- role of surgery
- palliative systemic treatment
- future directions?
- conclusions
- first-salvage treatment
- second and subsequent salvage treatment
- late relapse
- role of surgery
- palliative systemic treatment
- future directions?
- conclusions
# Conventional-dose Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agent(s)</th>
<th>Dose(s)</th>
<th>Day(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIP</strong></td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Day 1 - 5</td>
<td>Motzer 1990</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Day 1 - 5</td>
<td>Motzer 1990</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>75 mg/m²</td>
<td>Day 1 - 5</td>
<td>Motzer 1990</td>
</tr>
<tr>
<td><strong>VeIP</strong></td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Day 1 - 5</td>
<td>Loehrer 1998</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Day 1 - 5</td>
<td>Loehrer 1998</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>0.11 mg/kg</td>
<td>Day 1 +2</td>
<td>Loehrer 1998</td>
</tr>
<tr>
<td><strong>TIP</strong></td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Day 2 - 6</td>
<td>Motzer 2000</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Day 2 - 6</td>
<td>Motzer 2000</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175-250 mg/m²</td>
<td>Day 1</td>
<td>Motzer 2000</td>
</tr>
</tbody>
</table>

Repeated every 21 days for 4 cycles.
Vinblastine Plus Ifosfamide Plus Cisplatin as Initial Salvage Therapy in Recurrent Germ Cell Tumor

- Exclusion criteria: progression at <3 weeks after completion of first-line chemotherapy
- Minimal Follow-Up: 72 months
- Survival:
  - (2 year, 38%)
  - (3 year, 35%)
  - (7 year, 32%)
- Durable remission: 24%

n=135

Loehrerr et al, J Clin Oncol 1998
Ifosfamide- and Cisplatin-Containing Chemotherapy as First-Line Salvage Therapy in Germ Cell Tumors

- Inclusion or exclusion criteria: None
- Median Follow-Up: 52 months
- Median Survival: 18 months (range, 2 to 66+)
- Durable remission: 23%

n=56

Mccaffrey et al, J Clin Oncol 1999
Ifosfamide- and Cisplatin-Containing Chemotherapy as First-Line Salvage Therapy in Germ Cell Tumors

Table 3. Survival Stratified by Site and Prior Response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Continuously Alive</th>
<th>No.</th>
<th>%</th>
<th>Patients Relapse-Free</th>
<th>No.</th>
<th>%</th>
<th>Median Survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis primary and prior CR</td>
<td>11</td>
<td>65</td>
<td>7</td>
<td>41</td>
<td>Not reached</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extragonadal primary or prior IR</td>
<td>12</td>
<td>31</td>
<td>6</td>
<td>15</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McCaffrey et al, J Clin Oncol 1999
TIP as first Median FU
69 months
63% durable CR rate

2-year PFS:
65% (95% CI, 51% to 79%)

Only pts. With gonadal primary, CR or PRm- for more than 6 month were included

Kondagunta et al, JCO 2005
A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial

1y OS 70% (56 - 84%)

n=43

n= 26 pts. „good risk“
n= 17 pts. „poor risk“
2y PFS 73%
2y PFS 41%

Mead et al, Br J Cancer 2005
# High-dose Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
<th>Carboplatin</th>
<th>Etoposide</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indiana</strong></td>
<td>2x HDCT to be repeated after hematopoietic recovery</td>
<td>700 mg/m²</td>
<td>750 mg/m²</td>
<td>Days 1 - 3</td>
</tr>
<tr>
<td><strong>GTCSG</strong></td>
<td>1x VIP followed by 3x HCDT, to be repeated after 4 weeks</td>
<td>500 mg/m²</td>
<td>500 mg/m²</td>
<td>Days 1 - 3</td>
</tr>
<tr>
<td><strong>MSKCC</strong></td>
<td>2x TI followed by 3x HCDT, to be repeated after 4 weeks</td>
<td>AUC 8</td>
<td>400 mg/m²</td>
<td>Days 1 - 3</td>
</tr>
</tbody>
</table>

Indiana - Overall Survival

116/184 pts (63%) continuously disease-free
104/116 pts (90%) disease-free >2 years

n = 184 patients
sequential HDCT with 2 cycles CE
3 prognostic groups
median FU 48 ms

Einhorn et al, NEJM 2007
German germ cell cancer group (GTCSG) - PFS

- n = 211 pts.
- regimen:
  - arm A: sequential CE
  - arm B: single CEC

Significantly less toxicity with sequential HDCT (arm A);
PFS and OS not sign. different.

MSKCC - Progression free survival

- n = 107 pts.
- TI - CE regimen
  (3 cycles HDCT)
- 5-year DFS 47%
- 5-year OS 52%
- median FU 61 months

Feldmann et al, JCO 2010
Prognostic factors
In refractory germ-cell cancer
Problems with prognostic factor analyses in refractory germ-cell tumors

- Small number of patients, most often single center
- Not all patients received standard first-line treatment
- Inaccurate staging, outdated regimens
- Not really all patients had progressive disease
- Mixed cohort of first- and subsequent salvage treatments
- Frequent “inadequate” salvage management
Conventional-dose versus High-dose chemotherapy

High-dose versus conventional-dose chemotherapy as first-salvage treatment in patients with non-seminomatous germ-cell tumors: a matched-pair analysis

- Retrospective matched-pair analysis
- Matching factors:
  - Primary tumor location
  - Response to first-line treatment
  - Duration of response
  - HCG and AFP levels

Beyer et al, Annals of Oncology 2002
Conventional-dose versus High-dose chemotherapy

38 pairs of patients matched on 5 factors

Beyer et al, Annals of Oncology 2002
Conventional-dose versus High-dose Chemotherapy

A randomized trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumors.

3-year PFS
35% CDCT versus 42% HDCT P = 0.16

OS 53% (95% CI 46% to 59%)

single HDCT Carbo-PEC
n = 263 pts.
FU 45 months

Figure 1. Event-free survival.
Figure 3. Overall survival.

Pico et al, Ann Oncol 2005
Multicenter, multinational participation (Europe, USA, Canada)

Data collection of 1984 patients treated from 1990-2007

Retrospective data analysis of 1594 patients

All patients with first line salvage therapy

Conventional-dose as well as high-dose first line salvage

Strict inclusion criteria

Chart review

The international Prognostic Factor Study Group, JCO 2010
International Prognostic Factor Study Group

IPFSG developed a universally accepted prognostic model. Data consisted of 1,594 patients treated in 13 countries who progressed after initial cisplatin-based chemotherapy. Fifty-one percent of these patients received HDCT. Prognostic variables independent of treatment approach (CDCT or HDCT) included:

- Primary tumor site
- Response to first-line treatment,
- Progression-free interval between first-line therapy and relapse
- Tumor markers at relapse (AFP and HCG)
- Presence of liver, bone, or brain metastases at relapse

International Prognostic Factor Study Group (IPFSG)
Prognostic factors in refractory/relapsed patients

Table 4: Prognostic Score for Patients With Nonseminoma and Seminoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonadal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapleural</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonseminoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior response</td>
<td>CR/PR/ —</td>
<td>PTM+ /PSD</td>
<td>PD</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>PFH, months</td>
<td>&gt; 3</td>
<td>≤ 3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AFP salvage</td>
<td>Normal</td>
<td>≤ 1,000</td>
<td>&gt; 1,000</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HCG salvage</td>
<td>≤ 1,000</td>
<td>&gt; 1,000</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LBB</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Score sum (values from 0 to 10)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Regroup score sum</td>
<td>0</td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>5 or more</td>
<td>3</td>
</tr>
<tr>
<td>Add histology score points</td>
<td>pure seminoma = —1; nonseminoma or mixed tumors = 0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Final prognostic score</td>
<td>-1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=1594

Fig 1. Progression-free survival according to prognostic category (validation set plus patients with seminoma).

The International Prognostic Factor Study Group, JCO 2010
Salvage Treatment for testicular Cancer: CDCT vs HDCT

A Systemic Review of 59 Studies: CDCT(29) and HDCT(31)

Mean OS
CDCT 14.8 M
HDCT 24.09 M
P = 0.09

Petrelli F. Med Oncol 2017;34:133
Limitations

- Patient selection bias (given the nonrandom treatment allocation) potentially favoring HDCT.
- Wide variation in the CDCT regimens used, with some possibly inferior to others (e.g., TIP).
- Potential investigator bias in considering patients to progress earlier with CDCT than HDCT.

McHugh et al, Advances in Urology 2018
High-dose as intensification of first line salvage treatment?

Probably and should be considered especially in patients with adverse prognostic factors

However...

Do participation line TIGER
TIGER trial

- International collaboration among many centers in North America, Europe, and Australia
- Prospective phase III
- Will determine the optimal initial salvage chemotherapy approach in patients (N=420) with advanced GCT
- 67 (16%) patients accrued by 11/1/2017
- Expected to end in 2024
TIGER: international, prospective Phase III trial

N=420

TIP (n=210)

TI-CE (n=210)

Primary Endpoint
Overall Survival

Secondary Endpoints
- PFS
- Favorable RR (CR / PR-m)
- Toxicity & treatment-related mortality
- Validation of IPFSG model
- Biological correlates (SNP analyses)

Inclusion Criteria
- Histologically-confirmed GCT
- PD following 1st-line chemo
- ≥3 but ≤6 cycles of prior cisplatin-based chemo
- Adequate organ function for HDCT
- Any primary site

Stratification by IPFSG risk class and Continent

Sponsor: Alliance (USA, D. Feldman), EORTC (Europe, T. Powles), Movember
Summary conventional-dose versus high-dose as first line salvage

- two phase II trials favour conventional-dose salvage chemo in "good risk" patients
- one randomized trial failed to show superiority of high-dose dose over conventional-dose chemotherapy
- one large retrospective study showed superiority of high-dose over conventional-dose chemotherapy
- a prospective phase III trial is open (TIGER)
NCCN Guidelines Version 2.2020
Testicular Cancer - Nonseminoma

RECURRANCE

Second-Line Therapy

Early relapse (recurrence ≤2 years after completion of primary treatment)
- Clinical trial (preferred)
- Chemotherapy
  - Conventional-dose therapy (VeiP or TIP)
  - High-dose chemotherapy
- Consider surgical salvage if solitary site
- Recommend sperm banking if clinically indicated

Late relapse (recurrence >2 years after completion of primary treatment)
- Surgical salvage, if resectable (preferred)
- Clinical trial, if unresectable
- Chemotherapy
  - Conventional-dose therapy (VeiP or TIP)
  - High-dose chemotherapy
- Recommend sperm banking if clinically indicated

No prior chemotherapy
- Treat per risk status on TEST-11 and Recommend sperm banking

Prefered Regimens
- High-dose chemotherapy
- TIP = Paclitaxel/ifosfamide/cisplatin
- VeiP = Vinblastine/ifosfamide/cisplatin

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See NCCN Guidelines for Palliative Care.
ESMO Guidelines for 1st line salvage therapy (Seminoma)

- Treatment of relapse after adjuvant chemotherapy should be standard treatment according to the prognostic classification for metastatic disease.
  - Level of evidence: III
  - Strength of recommendation: B
  - Level of consensus: 93% (28) yes, 7% (2) abstain (30 voters)

Annals of Oncology 29: 1658-1686, 2018
doi:10.1093/annonc/mdy217
Published online 3 August 2018
ESMO Guidelines for 1st line salvage therapy (NON-seminoma)

- Treatment of relapse after adjuvant chemotherapy should be standard chemotherapy for metastatic disease.
  - Level of evidence: III
  - Strength of recommendation: B
  - Level of consensus: 90% (28) yes, 10% (3) abstain (31 voters)

- In patients with localised abdominal and marker-negative relapse, (NS)-RPLND is the preferred option for primary salvage treatment.
  - Level of evidence: III
  - Strength of recommendation: B
  - Level of consensus: 90% (28) yes, 10% (3) abstain (31 voters)

Annals of Oncology 29: 1658-1686, 2018
doi:10.1093/annonc/mdy217
Published online 3 August 2018
ESMO Guidelines for 1st line salvage therapy

- Treatment decisions about salvage chemotherapy are complex taking into account multiple factors, including primary tumour location, histology, response to first-line chemotherapy, location of metastases and tumour marker levels at the time of relapse or progression.
- Ideally, referred to specialized centers
- There is insufficient evidence to determine whether CDCT or HDCT produces superior outcomes as first-salvage chemotherapy
• first-salvage treatment options
• second and subsequent salvage treatment options
• late relapse
• role of surgery
• palliative systemic treatment
• future directions?
• conclusions
High-dose chemotherapy as second or subsequent salvage

- retrospective analysis
- treated 1989-2008 in Berlin and Marburg
- 71/534 pts identified, but 22 exclusions = 49 pts analyzed
- responses 55%, but high relapse rate
- 10/49 alive @ 48 months

Lorch, Beyer et al, Ann Oncol 2010
High-dose chemotherapy as second or subsequent salvage

- retrospective
- 2004-2014
- FU 3.3 y
- n = 364 pts.
- 303 pts. as 2nd-line
- 61 pts. as 3rd- or subsequent line
- 2-year PFS 60% (95% CI, 55% to 65%)
- 2-year OS 66% (95% CI, 60% to 70%)

Adra, Einhorn et al, JCO 2017
Summary second and subsequent salvage chemotherapy

- High-dose chemo might still be curative in second or even subsequent salvage treatment
- Randomized trials are lacking
NCCN Guidelines Version 2.2020
Testicular Cancer - Nonseminoma

**Recurrence**

- Complete response, negative markers
- Partial response, residual masses with normal AFP and beta-hCG levels
- Partial response residual masses with abnormal AFP and/or beta-hCG levels
- Elevated and rising AFP and/or beta-hCG level
- Elevated but stable AFP and/or beta-hCG levels
- Mildly elevated and normalizing AFP and/or beta-hCG levels
- Consider surgical resection of all residual masses

**Post Second-Line Therapy**

- Surveillance or Nerve-sparing bilateral RPLND in selected cases (category 2B)
- Surgical resection of all residual masses
- Residual embryonal, yolk sac, choriocarcinoma, or seminoma element
- Surveillance

See Third-Line Therapy (TEST-G)

See Follow-up for Nonseminoma, Table 8 (TEST-B 2 of 3)

For recurrence, See Third-line therapy (TEST-15)

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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b Mildly elevated, non-increasing AFP levels may not indicate presence of germ cell tumor.

Decisions to treat should not be based on AFP values >20 ng/mL. Further workup should be considered before initiating treatment for mildly elevated beta-hCG (generally >20 IU/L) since other factors, including hypogonadism and marijuana use, can cause false-positive results. **See Discussion**

kk RPLND is recommended within 4 weeks of CT scan and 7–10 days of marker measurement.

ll See Principles of Surgery for Germ Cell Tumors (TEST-H).

nn Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.

pp To assess response after treatment, CT with contrast of chest/abdomen/pelvis and any other sites of disease is recommended.

qq Recommend referral to a high-volume center.

uu It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.

vv Includes best supportive care and palliative care. **See NCCN Guidelines for Palliative Care.**
ESMO Guidelines for 2\textsuperscript{nd} line salvage therapy

- HDCT should be considered as second-salvage treatment in patients with a good performance status and adequate organ function who relapse or progress with systemic disease and/or increasing tumour markers after first salvage CDCT.
• first-salvage treatment options
• second and subsequent salvage treatment options
• late relapse
• role of surgery
• palliative systemic treatment
• future directions
• conclusions
Case

- **1988** diagnosis of a non-seminoma (embryonal plus teratoma), orchiectomy and primary RPLND pT1 pN1 M0
  
two cycles of adjuvant cisplatin, etoposide, bleomycin

- **2013** extensive abdominal relapse with AFP elevation
  => resection of local visceral surgeon
  => extensive surgery with R2 resection of undiff. tumor
  => transient normalization of AFP, but extensive post-OP complications
  => referred with rising AFP 295 ng/ml
Late relapse: 
Role of High-dose chemotherapy

- subgroup analysis of a phase III trial of HDCT as first line salvage treatment
- 35/216 late relapse pts.
- response 40% including one CR to chemo alone
- RTR could be done in 15/35 pts.
- 5 pts. without relapse or progression @ 5 years after HDCT plus surgery

Lorch, Beyer et al, J Urology 2010
- first-salvage treatment options
- second and subsequent salvage treatment options
- late relapse
- role of surgery
- palliative systemic treatment
- future directions
- conclusions
Role of Surgery

- salvage surgery rather than salvage chemotherapy in patients
  1. growing teratoma syndrome
  2. resectable late relapse GCC
  3. as desperation surgery

- residual tumor resection of all detectable residual masses in NSGCC mandatory for treatment success and long-term survival

- proportion of viable cancer in the specimen up to 70%
• first-salvage treatment options
• second and subsequent salvage treatment options
• late relapse
• role of surgery
• palliative systemic treatment
• future directions
• conclusions
# Subsequent and Palliative Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Dosing Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oechsle/Bokemeyer (2011) &quot;GOP&quot;</strong></td>
<td></td>
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</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m²</td>
<td>Day 1</td>
</tr>
<tr>
<td>Gemcitabin</td>
<td>800 mg/m²</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>80 mg/m²</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td><strong>Nicolai/Necchi (2009) &quot;CGP&quot;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50 mg/m²</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Gemcitabin</td>
<td>800 mg/m²</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>80 mg/m²</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td><strong>Einhorn (2007) &quot;GP&quot;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabin</td>
<td>1000 mg/m²</td>
<td>Day 1, 8 &amp; 15</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>100 mg/m²</td>
<td>Day 1, 8 &amp; 15</td>
</tr>
<tr>
<td><strong>Cooper/Einhorn (1995) &quot;Oral Etoposide&quot;</strong></td>
<td></td>
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</tr>
<tr>
<td>Etoposide</td>
<td>50 mg/m²</td>
<td>Day 1-21, every 4 weeks</td>
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## Subsequent and Palliative Regimens

<table>
<thead>
<tr>
<th>Regime</th>
<th>N pts</th>
<th>Pat. after HD-CTX</th>
<th>ORR</th>
<th>CR / PRm-</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Etoposide</td>
<td>21</td>
<td>29%</td>
<td>14%</td>
<td>0% / 14%</td>
<td>Miller 1990</td>
</tr>
<tr>
<td>Paclitaxel / Gemcitabine</td>
<td>28</td>
<td>36%</td>
<td>21%</td>
<td>10% / n.e.</td>
<td>Hinton 2002</td>
</tr>
<tr>
<td>Gemcitabine / Oxaliplatin</td>
<td>35</td>
<td>89%</td>
<td>46%</td>
<td>9% / 9%</td>
<td>Kollmannsberger 2004</td>
</tr>
<tr>
<td>Gemcitabine / Oxaliplatin</td>
<td>28</td>
<td>14%</td>
<td>32%</td>
<td>14% / n.e.</td>
<td>Pectasides 2004</td>
</tr>
<tr>
<td>Oxaliplatin / Irinotecan</td>
<td>18</td>
<td>0%</td>
<td>40%</td>
<td>22% / n.e.</td>
<td>Pectasides 2004</td>
</tr>
<tr>
<td>Oxaliplatin / Gemcitabine</td>
<td>18</td>
<td>22%</td>
<td>17%</td>
<td>5% / 5%</td>
<td>De Giorgi 2006</td>
</tr>
<tr>
<td>Gemcitabine / Paclitaxel</td>
<td>32</td>
<td>100%</td>
<td>31%</td>
<td>19% / 13%</td>
<td>Einhorn 2007</td>
</tr>
<tr>
<td>Paclitaxel / Oxaliplatin</td>
<td>26</td>
<td>n.e.</td>
<td>30%</td>
<td>0 / 4%</td>
<td>Theodore 2008</td>
</tr>
<tr>
<td>Gemcitabine / Oxaliplatin / Paclitaxel</td>
<td>41</td>
<td>78%</td>
<td>51%</td>
<td>5% / 46%</td>
<td>Bokemeyer 2008</td>
</tr>
</tbody>
</table>
- first-salvage treatment options
- second and subsequent salvage treatment options
- late relapse
- role of surgery
- palliative systemic treatment
- future directions?
- conclusions
Targeted Therapies


- Feldman DR, Turkula S, Ginsberg MS et al. Phase II trial of sunitinib in patients with relapsed or refractory germ cell tumors. Invest New Drugs 2010


- Feldman DR, Einhorn LH, Quinn DI et al. A phase 2 multicenter study of tivantinib (ARQ197) monotherapy in patients with relapsed or refractory germ cell tumors. Invest New Drugs 2013;


all studies with negative results
Treatment of CD30-Expressing Germ Cell Tumors and Sex Cord Stromal Tumors with Brentuximab Vedotin: Identification and Report of Seven Cases

- 7 patients with CD30-expressing testicular cancer
- 5 of them have with germ cell tumors
- Treated with brentuximab vedotin at initial doses of 1.8 or 2.4 mg/kg every 3 weeks
- Response assessed at cycles 2 and 4 and every 4 cycles thereafter

Albany, Einhorn, Garbo et al, The Oncologist 2018
Treatment of CD30-Expressing Germ Cell Tumors and Sex Cord Stromal Tumors with Brentuximab Vedotin: Identification and Report of Seven Cases

- One durable complete response
- One partial response
- Both germ cell tumors
- Brentuximab vedotin well tolerated

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor type</th>
<th>Sites of metastasis at enrollment</th>
<th>Best response</th>
<th>CD30 expression</th>
<th>H-score</th>
<th>CD30 cellular localization</th>
<th>HCG: mIU/mL</th>
<th>AFP: ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mixed GCT: EC, choriocarcinoma</td>
<td>Spleen, lung, iliacus muscle, periaortic</td>
<td>Partial response</td>
<td>90%</td>
<td>190</td>
<td>Membrane, cytoplasm</td>
<td>BL 5,571.0, min 45.3</td>
<td>N</td>
</tr>
</tbody>
</table>

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<th>AFP: ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Mixed GCT: EC, seminoma, teratoma</td>
<td>Lung: mediastinal, hilar, and supraclavicular lymph nodes</td>
<td>Complete response</td>
<td>100%</td>
<td>270</td>
<td>Membrane, cytoplasm, Golgi</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Albany, Einhorn, Garbo et al, The Oncologist 2018
n = 12 pts.
Pembrolizumab 200 mg i.v.
median number of Pembro 2 (range 1-8)
number of previous regimens 1-6

Results:
• no clinical activity for pembrolizumab
• no objective responses were observed
• 2 pts. with SD for 28 and 19 weeks, with continued rising AFP during treatment
• PD-L1 expression on tumor samples in only 2 pts.
• both PD-L1 pos. pts. with PD as best response

Adra et al, Ann of Oncology 2018
• first-salvage treatment options
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Conclusions I

- first, identify patients who do not need salvage chemotherapy
  - "growing teratoma"
  - resectable "late relapse"

- sequential HD carboplatin & etoposide is most frequently used outside clinical trials with acceptable toxicity

- TIGER addresses the question whether CDCT or HDCT as first line salvage is superior
Conclusions II

- HDCT can cure refractory resistant GCC even given as second or subsequent regimen
- unresectable late relapse can be treated either with CDCT or HDCT and additional complete resection of residual tumor
Conclusions III

- complete resection of residual masses is paramount for treatment success (in nonseminomas)
- no role for mono targeted therapies and checkpoint inhibitors so far, however, phase I/II trials are currently under way
- refer relapsed/refractory patients to expert centers
THANK YOU

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