Treatment of Refractory and Late Relapse Testicular Cancer Patients

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Disclosures:

No disclosures for this topic
Learning Objectives / Agenda

After reading and reviewing this material, the participant should be better able to understand:

- The clinical presentation of cisplatin-refractory disease
- Management options for cisplatin-refractory patients
- The presentation and biology of late recurrences
- The importance of a multi-disciplinary approach and the important role of surgery in the treatment of cisplatin-refractory disease and late recurrence
Cisplatin–refractory Disease and Late Relapse

Background

- Prognosis of relapse after second-line therapy is dismal
- Very small patient population
- Very few, small, non-randomized studies, including a heterogeneous patient population (early relapse, cisplatin-refractory, cisplatin-sensitive, late relapse....)
- No randomized studies to guide treatment decisions
Complexity of refractory and late relapse GCT patients

Decision making in the very rare patients with refractory GCT or late relapse is complex from deciding whether they have truly refractory disease or late relapse to therapeutic decisions regarding prognosis, the choice of the optimal treatment, timing and use of chemotherapy, incorporation of expert surgery and post chemotherapy management.

These patients can most benefit from being presented to an expert center with sufficient experience to assess and treat these cases.
Definitions:

• Absolutely cisplatin-refractory:
  Progression while on cisplatin-based chemotherapy

• Cisplatin-refractory:
  Progression within 4 weeks after completion of cisplatin-based chemotherapy

• Wider definition for refractory disease:
  Patients after failure of salvage high dose chemotherapy or several cisplatin-based regimens
Refractory GCT: case 1

- 28 year old pt
- 1/2007: respiratory distress
- CT: lung, liver, retroperitoneal and brain metastases
- US: 10 cm testicular mass
- HCG > 1 000 000  AFP 200  LDH 6x ULN
- Orchiectomy: teratoma plus choriocarcinoma
Refractory GCT: case 1

Initial diagnosis
Refractory GCT: case 1

• 1/2007 – 5/2007: VIP x 4
• Resection of brain lesion during chemotherapy → necrosis
• AFP / LDH normalized    HCG 13
Refractory GCT: case 1

After first-line chemotherapy
Refractory GCT: case 1

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Chemotherapy completed
Marker never normalized and increase within 4 weeks

Cisplatin-refractory!
Refractory GCT: case 1

What would you do?

• Further diagnostics e.g. PET scan?
• Standard dose salvage chemotherapy e.g. TIP?
• Salvage tandem high dose chemotherapy?
• Treatment with a non-cisplatin based regimen?
• Resection of as much disease as possible?
Salvage HDCT: Indiana Experience

N=184

Platinum refractory to first/second line standard chemotherapy: 21.7%

<table>
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<th>Overall cont. disease-free</th>
<th>116/184 (63%) after median F/U 48 months [25-112 months]</th>
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<tr>
<td>Cisplatin-refractory pts remaining disease free after HDCT</td>
<td>18/40 for median F/U 49 months [22-110 months]</td>
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High dose chemotherapy is a good option for patients refractory to first- or second line standard dose chemotherapy.
Refractory GCT: case 1

- 7/2007 – 10/2007: TIP x 2 + 2x HD-CT
- Marker normalisation
- Multiple residual sites
- No further surgery
Refractory GCT: case 1


Marker increase 2011, CT stable no change

Recurrence – free ever since

Nov 02 2011 36
Refractory GCT: case 2

- 49 year old pt
- 11/2011: testicular mass, painless
- HCG, AFP and LDH normal
- US: 6 cm testicular mass
- CT: 2.5 cm retroperitoneal lymph node metastasis

Orchiectomy: pure seminoma
Refractory GCT: case 2

January 2012

April 2012

EP x 4
Refractory GCT: case 2

Early progression

April 2012  

June 2012
What would you do?

- Further diagnostics e.g. PET scan?
- Standard dose salvage chemotherapy e.g. TIP?
- Salvage tandem high dose chemotherapy?
- Treatment with a non-cisplatin based regimen?
- Resection of the growing lesion?
- Radiation of the growing lesion?
Salvage ("desperation") surgery

- N = 48
- Surgery for chemo-refractory disease
- RPLND x 33, thoracotomy x 6, thoracoabdominal x 3, multiple asynchronous resections x 6
- 79% grossly rendered disease – free with 60% achieving serologic complete remission
- 10 pts (21%) continuously disease-free
- 6 additional pts disease free after additional therapy

Potentially curative approach
Refractory GCT: case 2

Patient underwent RPLND

Pure vital seminoma

Recurrence free ever since
Prognosis of Refractory Patients after Salvage High-dose Chemotherapy

• Appr. 50 % of pts. will receive palliative chemotherapy after relapse from high-dose chemotherapy
• RR < 20 %
• Median survival: 8–12 months for treated pts vs. 3 months for untreated pts
• Historically 5 % long term remissions: resection ± chemotherapy
• Only significant prognostic factor: Interval HD-Ctx \( \rightarrow \) post-HD-Ctx < 12 months (p = 0.04)

Porcu / Einhorn J Clin Oncol 2000

• Only over the past 5–8 years recommendations based on small clinical studies with new agents
### Drugs with minor / no activity in refractory GCT

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<td>Puc 1995</td>
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<td>Kollmannsberger 2000</td>
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<td>Kollmannsberger 2002</td>
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<td>Kondagunta 2004</td>
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<td>Oechsle 2007</td>
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Kollmannsberger / Bokemeyer Exp Opinion Pharm 2008
## Chemotherapy of patients with cisplatin-refractory GCT

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<td>Gemcitabine(^3)</td>
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<td>Oxaliplatin(^4)</td>
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<table>
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<th>Combinations</th>
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<tr>
<td>Paclitaxel/Gemcitabine(^5)</td>
<td>21%</td>
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<tr>
<td>Gemcitabine/Oxaliplatin(^6)</td>
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<td>Gemcitabine/Oxaliplatin(^7)</td>
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All studies with long-term survivors, in particular after complete resection of residual lesions

\(^1\)Einhorn JCO 1991  \(^2\)Motzer JCO 1994  \(^3\)Einhorn JCO 1999  \(^4\)Kollmannsberger JCO 2002  
\(^5\)Hinton JCO 2002  \(^6\)Kollmannsberger JCO 2004  \(^7\)Pectasiadis Ann Oncol 2004
Long term outcome after chemotherapy for refractory germ cell tumors

2 GTCSG studies: Gemcitabine/Oxaliplatin (GO) and Gemcitabine/Oxaliplatin/Paclitaxel (GOP)

- N = 76 (35 GO and 41 GOP)
- Median survival for all patients: 8 months
- 8/76 alive > 2 years (11%)
- 1 GO and 7 GOP patients are relapse free with a OS > 33 mo
- All but one had chemotherapy plus subsequent surgery

Approx. 10% of patients may be cured

Surgery is a critical component of the overall treatment strategy

Kollmannsberger / Bokemeyer et al JCO 2004;
Bokemeyer / Kollmannsberger et al Ann Oncol 2008;
Ochsle / Kollmannsberger / Bokemeyer et al Eur Urol 2011
Salvage (“desperation”) surgery

- Surgery for chemo-refractory disease
- Declining or persistent tumor markers after chemotherapy
- Slowly rising markers after initial response to chemotherapy
- Rising markers with resectable disease after exhausting all chemotherapy options
- Platinum refractory patients with resectable disease

Complete resection most important single parameter for favorable outcome

Up to 50% long term survivors

Albers et al J Urol 2000
www.esmo2012.org
Treatment of refractory GCT

Progression while on or within 4 weeks after completion of cisplatin-based chemotherapy / Progression after high dose salvage chemotherapy

If no prior salvage high dose chemotherapy:

- Salvage high dose chemotherapy
  - Resection of residual disease
  - Relapse

If prior salvage high dose chemotherapy:

- Non-cisplatin based regimen, e.g., oxaliplatin/gemcitabine
  - Resection of residual disease
  - Relapse
Conclusions

- Patients with cisplatin refractory disease exhibit a very poor prognosis and should be considered for clinical trials.

- Surgery remains an essential part of any treatment strategy for cisplatin-refractory disease or late recurrences.

- The identification of new active drugs remains a priority.

- The increasing understanding of the pathogenesis, and molecular changes in testicular cancer as well as of cisplatin resistance will translate into improvements in treatment and prognosis for our patients.

- International cooperation is needed to test new strategies.

- Due to the complexity of relapsed GCT and the need for experienced multidisciplinary teams, patients should be treated at experienced centers!
Definition of Late Relapse

• Different definitions / patient populations exist:
  – Inclusion of “late” relapse in stage I nonseminomas
  – Inclusion of “late” relapse in stage I seminomas
  – Inclusion of late relapse of extragonadal GCT
  – Exclusion of late relapse from extragonadal GCT
  – ..........

Late Relapse

Treatment of Chemotherapy–Naive Patients

- Stage I seminoma (surveillance, adjuvant RT, carboplatin)
- Stage IIA seminoma (RT)
- Stage I Non seminoma (RPLND or surveillance)
- Stage II nonseminoma RPLND without adjuvant chemotherapy

Cisplatin based chemotherapy (VIP / TIP / VeIP…) and surgery of residual disease

Very good prognosis

Late Relapse
Characteristics

Definition: Recurrences at least 2 years after successful first-line treatment for metastatic disease

- 1–4% of pts develop late recurrences
- Incidence in nonseminoma (3–4%) > seminoma (1–2%)
- Retroperitoneum is most common location (≥ 50%)
- Lung (nonseminoma) and mediastinum (seminoma) are second most common location
- Time to relapse varies greatly (2–40 years)
- 60–70% are diagnosed because of symptoms
- Elevated AFP common (70%), HCG rarely elevated

Oldenburg et al JCO 2006; George et al JCO 2003; Shahidi et al Cancer 2002
Late Relapse: Case 1

- 37 year old patient
- Initial dx at age 16 with disseminated nonseminoma, poor risk with liver, lung, retroperitoneal metastases
- Initial therapy: Cisplatin-based chemotherapy + RPLND.
- 2002: intermittent abdominal cramps, CT normal
- Intermittent abdominal pain till 2006
- Sept. 2006: CT abdo–pelvis → no abnormalities
Late Relapse: Case 1

• March 2007: Pain constant, now nausea, weight loss

• U/S: large mass around aorta

• TUM April 4th: AFP 180 000, LDH 335 (ULN 220), HCG, CEA, CA19–9 normal

• CT Chest/abdo/pelvis
Late Relapse: Case 1

Multiple Lung metastases

Large retrop. tumor

April 2007
Late Relapse
Differential Diagnosis

- Metastases from a new contralateral primary
- A new primary EGGCT
- Metastases from a new non–GCT primary
- Transformed teratoma
- Growing teratoma

Biopsy required if not resectable !!

Nichols CR Semin Surg Oncol 1999
Late Relapse: Case 1

- New primary GCT ????
  - US testicle entirely normal

- Other malignancy ?
  - But AFP high
  - Unlikely at that age
  - Biopsy
Late Relapse
Pathology

- Teratoma most common
  - Can “leak” low amounts of AFP/HCG
- Yolk Sac most common active germ cell subtype but can have atypical appearance
- All other GCT subtypes are possible
- Transformed teratoma (5–15%)
  - Sarcomas, adenocarcinomas, undifferentiated carcinoma

➢ If in doubt → test for presence of i(12p)
➢ expert pathology review recommended

www.esmo2012.org
Late Relapse: Case 1

• Biopsy: embryonal carcinoma/Yolk Sac

• What would you do?
  – Treatment with VIP
    (Etoposide/Ifosfamide/Cisplatin)
  – Treatment with BEP
    (Bleomycin/Etoposide/Cisplatin)
  – Treatment with a non-cisplatin containing regimen e.g. oxaliplatin/gemcitabine
  – High dose chemotherapy
Late Relapse
Adverse Prognostic Factors

Symptoms at presentation and multifocality are associated with a poor prognosis

- Complete vs. incomplete resection
- Prior CTx vs. no prior Ctx

Sharp et al JCO 2008
www.esmo2012.org
Late Relapse
Management – Chemotherapy

- Chemotherapy is given according to histology
  - Platinum based chemotherapy (e.g. TIP) for germ cell histologies

- Frequently chemotherapy-resistant

- High-dose chemotherapy remains controversial
  - Very few data
  - Long-term survivors rare but have been reported
  - Resection as an important part of the overall treatment strategy

- Responses to chemotherapy are infrequent and usually short-lived

- Chemotherapy alone (without surgery) induced long-term survival is extremely rare

Ronnen et al JCO 2005
Lorch et al Ann Oncol 2010
Late Relapse: Case 1 – Staging after 2 Cycles

April 2007

June 2007

VIP x 2
Late Relapse: Case 1 - Staging after 2 Cycles VIP

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Cycle 1: L85069, L85212 - AFP <1.2 IU/L
Cycle 2: L90605, L86422, L88112, L87327, L79496, L79172 - AFP >300000 ug/L
Late Relapse: Case 1

• What would you do?
  – Treatment with BEP (Bleomycin/Etoposide/Cisplatin)
  – Treatment with a non-cisplatin containing regimen e.g. oxaliplatin/gemcitabine
  – High dose chemotherapy
  – Attempt resection?
  – Palliative care
Late Relapse

Management – Surgery

• Surgery is the most important component of treatment in patients with late-relapsing TC
  – Surgical resection should be aggressively pursued whenever possible

• Treatment at high volume / expert centers is highly recommended

• No adjuvant chemotherapy after complete resection

• Postchemotherapy RPLND for residual disease (> 1 cm) the most important preventative strategy

Sharp et al JCO 2008
Ronen et al JCO 2005
Late Relapse: Case 1

• Gemcitabine/oxaliplatin x 1 cycle: May/June 2007
  – Acute severe neuropathic reaction day 1 to oxaliplatin

• Gemcitabine 2 cycles

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Late Relapse: Case 1

• What would you do?
  – Treatment with BEP (Bleomycin/Etoposide/Cisplatin)
  – Treatment with different non-cisplatin containing regimen e.g. paclitaxel
  – High dose chemotherapy
  – Clinical trial
  – Palliative care
## Late Relapse: Case 1

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- **DOD March 2008**

Start sunitinib
Late Relapse: Case 2

- 38 year old pt
- 2002: good prognosis NS
- AFP 459, HCG normal, LDH normal
- CT scan: retroperitoneal LN 4 cm

Orchiectomy: Yolk Sac, Embryonal carcinoma, Teratoma

BEP x 3 → marker negative PR

RPLND: Mature Teratoma, completely resected
Late Relapse: Case 2

Recurrence –free until 2011

2011: AFP 3100

Isolated pelvic lymph node
Late Relapse: Case 2

• What would you do?
  – Treatment with VIP or TIP
  – Treatment with a non-cisplatin containing regimen e.g. oxaliplatin/gemcitabine
  – High dose chemotherapy
  – Resection of disease
  – Palliative care
Late Relapse: Case 2

Resection: left and right-sided pelvic, paracaval, and periaortic LAD

Pathology: solitary lymph node, Yolk Sac histology
no other nodes involved
Late Relapse: Case 2

• What would you do?
  – Treatment with standard dose cisplatin-based chemotherapy x 4 cycles e.g. VIP?
  – Treatment with standard-dose cisplatin-based adjuvant chemotherapy x2 cycles?
  – Treatment with different non-cisplatin containing regimen e.g. paclitaxel?
  – High dose chemotherapy?
  – Watch without further therapy?
Late Relapse: Case 2

Resection: left and right-sided pelvic, paracaval, and periaortic LAD

Pathology: solitary lymph node, Yolk Sac histology
no other nodes involved

Recurrence free since
Late Relapse

Treatment of marker-only disease

- PET scan to identify the site of evolution in a minority of patients
- Detection by CT scan in the majority of patients
- Withhold any treatment until the site of evolution is demonstrated and manageable by surgical excision

Surgery ± chemotherapy whenever feasible

Late relapse

Malignant Transformation

- Rare, estimated to occur in 3–6% of pts with teratoma components
- Limited literature, mostly small series
- Poor prognosis
- Treatment according to histology
- Cisplatin–based GCT chemotherapy of limited benefit

Resection as the treatment of choice whenever possible
Late Relapse

CONCLUSION (1)

• Late relapse is rare (<5% in modern series)
• More frequent in advanced non seminoma
• Importance of postchemotherapy resection of residual disease:
  – Risk of growing teratoma
  – Risk of transformed teratoma
  – More often yolk sac tumor
• Largely resistant to chemotherapy except for chemo-naive patient
• Salvage surgery is the mainstay of therapy
• Approx. 20–60% long term survivors depending on complete resectability
• Referral to expert centers strongly recommended
Late Relapse

CONCLUSION (1)

• Late relapse is rare (< 3–5% in modern series)

• More frequent in advanced non seminoma

• Importance of postchemotherapy resection of residual disease:
  – Risk of growing teratoma
  – Risk of transformed teratoma
  – More often yolk sac tumor

• Targeted agents have standard role in the treatment of these tumors at the present time
Late Relapse

CONCLUSION (2)

• Largely resistant to chemotherapy except for chemo-naive patient

• Salvage surgery is the mainstay of therapy

• Approx. 20–60% long term survivors depending on complete resectability

• Referral to expert centers strongly recommended