EXTRAGONADAL GERM CELL TUMOURS

Effective Date: April 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Germ cell tumours (GCTs) are one of the most common cancers among young adult men. An extragonadal GCT is, by definition, a germ cell neoplasm displaying one of the histologies associated with gonadal origin, but located outside the gonads. Extragonadal GCTs are relatively uncommon, but represent 1 to 5% of all GCTs. Non-central nervous system extragonadal GCTs are found in a variety of anatomic locations, but most commonly affect the mediastinum and retroperitoneal.

The mediastinum is the most common anatomic site for extragonadal germ cell tumours in adults. Data on GCT etiology suggest that mediastinal GCTs comprise approximately 54% of all extragonadal GCT cases, while retroperitoneal GCTs comprise the remaining 45%. The majority of these cases occur in males aged 20 to 40 years. When treated with induction chemotherapy, with or without secondary surgery, patients with pure seminomatous extragonadal GCTs have a long term cure rate of almost 90%, irrespective of the primary tumour site. Patients with mediastinal non-seminoma have a five-year survival rate of 45%, whereas patients with retroperitoneal primaries have a five-year survival rate of 62%.

GUIDELINE QUESTION

What are the appropriate management strategies for patients with primary mediastinal or retroperitoneal germ cell tumours?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

The Pubmed database was searched using the terms (retroperitoneal OR mediastinal) AND germ cell AND primary, published between 1946 and 2012 April. Results were limited to clinical trials, studies in humans, meta-analyses, and practice guidelines. The Medline database was then searched for relevant literature using the MeSH terms “Neoplasm, germ cell and embryonal” with subheadings drug therapy, radiotherapy, therapy, and surgery, combined with “extragonadal.” Results were limited to literature published between 1946 and 2012 April. Studies involving fewer than ten patients with extragonadal germ cell tumours, as well as single case studies, were excluded.

Websites of the following guideline developers were searched for relevant guidelines: National Comprehensive Cancer Network (NCCN), British Columbia Cancer Agency (BCCA), European Society of Medical Oncology (ESMO), National Institutes of Health and Clinical Excellence (NICE), American Society of Clinical Oncology (ASCO), Scottish Intercollegial Guidelines Network (SIGN), Cancer Council Australia (CCA) and Cancer Care Ontario (CCO).
TARGET POPULATION

These recommendations apply to postpubertal patients with primary mediastinal or retroperitoneal germ cell tumours.

RECOMMENDATIONS

Diagnosis:

- If a patient presents with undifferentiated adenocarcinoma of unknown origin, copy number of chromosome 112p should be performed.
- Lactate dehydrogenase (LDH), alpha fetoprotein (AFP) and gonadotropin (hCG) should be assessed.
- Patients should be classified and treated based on prognosis.\(^1\)

Table 1. Prognostic factors for germ cell tumours.

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Non-seminoma</th>
<th>Seminoma</th>
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<tr>
<td>good</td>
<td>Primary extragonadal retroperitoneal and low markers: AFP&lt;1,000ng/ml and (\beta)-HCG&lt;1,000ng/ml (&lt;5,000 IU/l) and LDH&lt;1.5 x normal level and no non-pulmonary visceral metastases</td>
<td>Any primary localization and any marker level</td>
</tr>
<tr>
<td>intermediate</td>
<td>Primary extragonadal retroperitoneal and AFP 1,000-10,000ng/ml and/or (\beta)-HCG 1,000-10,000 ng/ml (5,000-50,000 IU/l) and/or LDH 1,5 – 10 x normal level and no non-pulmonary visceral metastases</td>
<td>Any primary localization and presence of non-pulmonary visceral metastases (liver, CNS, bone, intestine) and/or high markers</td>
</tr>
<tr>
<td>poor</td>
<td>Primary mediastinal germ cell tumour with or without testis or primary retroperitoneal tumour and presence of non-pulmonary visceral metastases (liver, CNS, bone, intestine) and/or &quot;high markers&quot; AFP &gt;10,000 ng/ml, (\beta)-HCG &gt;10,000 ng/ml (50,000 IU/l) or LDH &gt;10 x normal level</td>
<td>N/A</td>
</tr>
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Management:

1. Patients should be considered for clinical trials.
2. Bleomycin, etoposide and cisplatin (BEP) or etoposide, ifosfamide, cisplatin (VIP) is recommended as first-line chemotherapy, with the number of cycles given based on risk category.
3. For failure or relapse on either of these regimens and good risk disease, high dose chemotherapy and peripheral blood stem cell transplantation can be given. Recommended agents for high dose chemotherapy include ifosfamide, vinblastine, carboplatin, etoposide and paclitaxel.
4. Patients who are classified as poor risk at relapse should be considered early for high dose chemotherapy and peripheral blood stem cell transplantation, as they may not be well enough to consider this treatment in the third line setting.
5. Patients with mediastinal GCTs who relapse have poor prognosis. Transplant should not routinely be offered to these patients. However, depending on the results from salvage chemotherapy, patient performance status, individual factors and patient’s desire to pursue the transplant, it may be considered only after an honest discussion between the clinician and patient as the chance of long term remission and cure are very low.

6. After the completion of chemotherapy, strong consideration for retroperitoneal lymph node dissection should be given in those patients with retroperitoneal primary GCTs.

7. After the completion of chemotherapy, surgery to resect any residual masses should be strongly considered in those patients with mediastinal primary GCTs.

Table 2. Suggested follow up schedule for germ cell tumours.  

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical examination and diagnostics</th>
<th>Frequency of exam (months)</th>
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<tr>
<td></td>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>good prognosis</td>
<td>LDH, AFP, HCG, clinical exam</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>X-ray of the chest or CT scan of</td>
<td>3-6*</td>
</tr>
<tr>
<td></td>
<td>chest (if supradiaph. disease)</td>
<td></td>
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<tr>
<td></td>
<td>CT scan of the abdomen/pelvis</td>
<td>3</td>
</tr>
<tr>
<td>intermediate and poor</td>
<td>LDH, AFP, HCG, clinical exam</td>
<td>3</td>
</tr>
<tr>
<td>prognosis</td>
<td>X-ray of the chest or CT scan of</td>
<td>3-6*</td>
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<tr>
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<td></td>
<td>CT scan of the abdomen/pelvis</td>
<td>3</td>
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* depending on the presence of intrathoracic disease

DISCUSSION

Diagnosis

Data from an international series of 635 patients with extragonadal GCTs (54% had mediastinal primary GCTs and 45% had retroperitoneal primary GCTs) who were treated from 1975 to 1996 at 11 cancer centers was analyzed. The most common symptoms at initial presentation in patients with mediastinal GCTs included dyspnea (25%), chest pain (23%) and cough (17%), fever (13%), weight loss (11%), vena cava occlusion syndrome and fatigue or weakness (6%). For patients with retroperitoneal primary GCTs, most common symptoms were abdominal-related (29%) and back pain (14%), followed by weight loss (9%), fever (8%), and vena cava or other thrombosis (9%). Around 50-75% of patients with non-seminoma extragonadal GCTs have elevated AFP and iso-chromosome i12p. Approximately 40% of patients with mediastinal seminoma and non-seminoma and those with retroperitoneal seminoma have elevated hCG. A higher average percentage (about 70%) of patients with retroperitoneal non-seminoma present with elevated hCG levels. Patients should be classified and treated based on prognosis.

Management

Chemotherapy

All patients presenting with extragonadal germ cell tumours should be considered for enrollment in clinical trials. Bleomycin, etoposide and cisplatin (BEP) or etoposide, ifosfamide, cisplatin (VIP) is recommended as first-line chemotherapy, with the number of cycles given based on risk category. The recommendation
is in line with that of other guidelines and reviews.²,⁹,¹¹,¹² VIP should be considered for those patients who cannot tolerate bleomycin. A phase III trial by Motzer et al. (2007) randomized patients to receive either 4 cycles of BEP or 2 cycles of BEP followed by 2 cycles of cisplatin, etoposide, cyclophosphamide (CECP) and stem cell transplant. Of the 219 patients included in this study, 11 had retroperitoneal primary GCTs and 58 had mediastinal primary GCTs. Complete response to treatment was similar between the two groups (55% for BEP versus 56% for CECP), as was 2-year overall survival (72% for BEP versus 71% for CECP). However, gastrointestinal and hepatobiliary toxicity was lower in the BEP group (19% versus 42% and 9% versus 24%, respectively).¹³

Nichols et al. (1998) conducted a randomized trial of 304 patients with advanced, disseminated germ cell tumours. Patients received either four cycles of BEP or VIP. Complete remission rate (37% VIP versus 31% BEP) and 2-year overall survival rate (74% VIP and 71% BEP) were not significantly different. However, the use of ifosfamide instead of bleomycin led to significantly higher genitourinary and hematologic toxicity.¹⁴ The final analysis of Eastern Cooperative Oncology Group protocol E3887 had similar results. After a median follow-up of 7.3 years, patients had similar progression free survival and overall survival rates. For patients treated with BEP, overall survival was 57% and progression free survival 49%, versus 62% and 56% in patients treated with VIP. Hematologic toxicity was greater in the ifosfamide arm in this study as well.¹⁵

For failure or relapse on either of these regimens and good risk disease, high dose chemotherapy (HDCT) and peripheral blood stem cell transplantation can be given. Recommended agents for HDCT include ifosfamide, vinblastine, carboplatin, etoposide and paclitaxel. Patients who are classified as poor risk at relapse should be considered early for HDCT and peripheral blood stem cell transplantation, as they may not be well enough to consider this treatment in the third line setting. Hartmann et al. (2001) conducted a multi-centre retrospective review of 142 patients with relapsed non-seminomatous extragonadal germ cell tumours who received platinum-based chemotherapy as first-line treatment. Patients were treated at relapse with combinations of cisplatin, ifosfamide, vinblastine, etoposide, carboplatin and paclitaxel, and 34% of patients were treated with HDCT followed by autologous bone marrow transplantation.¹⁶ At 45 months follow-up, 19% of patients (n=27) were alive without evidence of disease; 17 of those were treated at relapse with conventional chemotherapy and 10 were treated with HDCT. For patients with retroperitoneal primaries, 32% and 12% of those with mediastinal primaries treated with HDCT achieved were alive without any evidence of disease at 45 months. Of these patients, 44% of them also received surgery post-HDCT.¹⁶

A randomized phase III trial of 280 patients with relapsed poor prognosis GCTs compared 4 cycles of cisplatin, ifosfamide, and etoposide (A) with 3 cycles followed by HDCT with etoposide, carboplatin and cyclophosphamide and haematopoietic stem cell support (B). No significant improvements in the HDCT group were observed in regards to 3-year event free survival (35% versus 42%, p=0.16) or overall survival (53% versus 59%).¹⁷ Feldman et al. (2010) reported the outcomes of 107 patients with poor prognosis GCTs (such as those with extragonadal primaries) who failed first line chemotherapy and were subsequently treated with paclitaxel and ifosfamide, followed by high-dose carboplatin and etoposide (TICE) with stem cell transplant. Five-year disease free survival was 47% for these patients, and OS was 52% (median follow-up 61 months).¹⁸ Lorch et al. (2010) conducted a trial of HDCT in late relapse GCTs, defined as relapse after 2 years from completion of cisplatin-based chemotherapy. Patients were treated with HDCT followed by resection where possible. At a median follow-up of 5.6 years, 14% of patients had no evidence of disease progression.¹⁹
Patients with mediastinal GCTs who relapse have poor prognosis. Transplant should not routinely be offered to these patients. However, depending on the results from salvage chemotherapy, patient performance status, individual factors and patient’s desire to pursue the transplant, it may be considered only after an honest discussion between the clinician and patient as the chance of long term remission and cure are very low. Hidlago et al. (1997) looked specifically at patients with mediastinal non-seminoma treated with cisplatin-based chemotherapy and considered for residual mass resection in their retrospective review of patient records. Fifteen patients had disease confined to the mediastinum, and 12 had metastatic disease. Eleven patients (40.7%) became disease free with initial treatment; 4 of these patients had received only platinum-based chemotherapy, 1 surgery followed by adjuvant chemotherapy, and 6 chemotherapy followed by surgery. The remaining patients had only partial or no response to initial treatment, and 11 received salvage treatment to which none responded. This led the authors to conclude that in the case of mediastinal non-seminoma, the achievements of a disease-free status after initial treatment are likely to be cured.20

**Surgery in extragonadal GCTs**

In retroperitoneal germ cell tumours, strong consideration for retroperitoneal lymph node dissection should be given after the completion of chemotherapy (recommendation #6). Consideration should also be given to the resection of any residual masses in mediastinal primary GCTs (recommendation #7).

Gerl et al. (1996) reviewed the medical records of 51 patients with extragonadal germ cell tumours (n=35 retroperitoneal primary, n=16 mediastinal primary) treated with platinum-based chemotherapy and surgery. Thirty five patients had seminoma, and the remaining 16 non-seminoma. Fifty percent of patients with mediastinal primary non seminoma had no evidence of disease at a median of 96 months, whereas 65% of patients with retroperitoneal non seminoma had no evidence of disease at a median of 39 months. Those patients with seminoma extragonadal tumours survived with no evidence of disease constituted 96% of all seminoma patients at a median of 66 months. Goss et al. (1994) documented their 14 year experience treating a total of 40 patients with extragonadal GCTs at 4 University of Toronto teaching hospitals. After combined modality therapy, 53% of mediastinal non seminomas achieved complete remission at a median 70 months, whereas 88% of mediastinal seminomas survived with no evidence of disease at a median 45 months.22

Kesler et al. (2008) reported a 25-year single institution experience of post-chemotherapy surgery for 158 patients with mediastinal primary non-seminoma GCTs. Intra-operative deaths occurred in 6% of patients, 90% of which were due to respiratory failure. Post-operative complications occurred in 18% of patients. Interestingly, none of the patients that received a chemotherapy regimen containing bleomycin had respiratory complications during or after surgery.23 A retrospective study of 75 patients with primary mediastinal non-seminomatous GCTs was conducted by Ganjoo et al. (2000). All patients received platinum-based chemotherapy, and 62 (83%) underwent post-chemotherapy resection. Post-chemotherapy pathology was found in both a multivariate and univariate analysis to be the most important predictor of survival (p<0.001), with 93% of those patients with necrosis continuously had no evidence of disease, whereas only 31% of those with viable germ cell cancer did at a median follow-up of 22 months. In total, 69.3% of patients had no evidence of disease at 22 months.24
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFP</td>
<td>alpha fetoprotein</td>
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<tr>
<td>BEP</td>
<td>bleomycin, etoposide, cisplatin</td>
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<tr>
<td>GCT</td>
<td>germ cell tumour</td>
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<tr>
<td>hCG</td>
<td>gonadotropin</td>
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<tr>
<td>HDCT</td>
<td>high dose chemotherapy</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
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<tr>
<td>TI-CE</td>
<td>paclitaxel, ifosfamide, cisplatin, etoposide</td>
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<tr>
<td>VIP</td>
<td>etoposide, ifosfamide, cisplatin</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of AHS, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES