Medical Treatment of Advanced Testicular Cancer

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Context The medical treatment of advanced testicular germ cell tumors has changed over the past 30 years, with long-term survival now achieved in the majority of patients. Clinicians need to be familiar with the available treatment regimens for testicular cancer and their associated toxic effects.

Objective To review the treatments used for advanced testicular germ cell tumors and their associated short-term and long-term complications.

Evidence Acquisition A search was performed of all English-language literature (1966 to October 2007) within the MEDLINE database using the terms neoplasms, germ cell, or embryonal or testicular neoplasms restricted to humans, drug therapy, complications, and mortality. The Cochrane Register of Controlled Trials Databases (through October 2007) was also searched using the terms testicular cancer or germ cell tumors. Bibliographies were reviewed to extract other relevant articles. One hundred eighty-six articles were selected based on pertinence to advanced testicular cancer treatment, associated complications, and late relapses with an emphasis on randomized controlled trials.

Data Synthesis The treatment of advanced testicular germ cell tumors with cisplatin combination chemotherapy is based on risk stratification (good, intermediate, or poor prognosis) according to pretreatment clinical features of prognostic value. Clinical trials have demonstrated that approximately 90% of patients classified as having a good prognosis achieve a durable complete remission to either 4 cycles of etoposide and cisplatin or 3 cycles of cisplatin, etoposide, and bleomycin. Complete responses are achieved less frequently for patients with intermediate- and poor-risk germ cell tumors, in whom 4 cycles of bleomycin, etoposide, and cisplatin remains the standard of care. Second- and third-line programs, including high-dose chemotherapy, also have curative potential. Chronic toxicities associated with therapy include cardiovascular disease, infertility, and secondary malignancies. Late relapses may also occur.

Conclusions Clinical trials have led to evidence-based treatment recommendations for advanced testicular cancer based on risk stratification. Clinicians should be familiar with the potential complications of these therapies.

See also Patient Page.

CME available online at www.jamaarchivescme.com and questions on p 706.

BACKGROUND

GCT Histology and Genetics

Germ cell tumors are malignancies of primordial germ cells, the cells destined to become spermatozoa. With neoplastic transformation, these cells take on a variety of histologies, reflect-
ing their broad differentiating capability. Germ cell tumors are characterized by the acquisition of extra copies of chromosome 12p, most commonly through an isochromosome (i12p). Several candidate genes have been localized to 12p and may be important to the pathogenesis of GCT. In addition, 10% to 20% of seminomas may harbor activating mutations in the c-KIT gene.

Germ cell tumors are also frequently triploid or hypotetraploid in DNA content, suggesting that other genetic aberrations play a role in their pathogenesis.

Germ cell tumors are broadly separated into 2 groups, seminomas and nonseminomas, each comprising approximately 50% of cases. Almost all seminomas are curable with orchectomy with or without radiation; only occasionally do these cancers require chemotherapy. Nonseminomas consist of several different histologies (embryonal cell carcinoma, yolk sac tumor, choriocarcinoma, teratoma), each displaying a different stage of embryonic or extraembryonic differentiation with varying tumor marker profiles. Teratoma, composed of 2 or more embryonic cell layers, lacks the potential to metastasize but can sometimes transform into a somatic malignancy (ie, sarcoma) and take on aggressive behavior. Nonseminomatous GCTs are less sensitive to radiation than seminomas and when metastatic, frequently require both chemotherapy and surgery.

**Historical Perspective on Treatment and Risk Group Stratification**

A major advance in chemotherapy for testicular GCT was the introduction of cisplatin in the mid 1970s. A landmark trial reported in 1977 used a regimen of cisplatin, vinblastine, and bleomycin for 4 cycles followed by 21 months of maintenance vinblastine. The complete response rate increased from a historical control of 25% to more than 80% with the use of this regimen in combination with surgery. The high complete response rate was associated with moderately severe toxic effects, so further efforts focused on reducing toxicity and duration of therapy without compromising efficacy. Changes included eliminating maintenance therapy, substituting etoposide for vinblastine, and eliminating or reducing the dose of bleomycin.

By the late 1980s, investigators realized that certain clinical and tumor features could predict the likelihood of patient response to standard chemotherapy regimens. Several algorithms were developed to stratify patients into “good” or “poor” prognostic groups and were incorporated into clinical trials in order to test treatment strategies in specific patient populations. Differences between the algorithms made it difficult to compare trial results. The International Germ Cell Cancer Collaborative Group (IGCCC) was formed, and a universal classification scheme was developed. In this stratification system, patients are separated into good-, intermediate-, and poor-prognostic groups according to predicted outcome to cisplatin-combination chemotherapy, based on histology, primary site, sites of metastasis, and serum tumor marker elevation (Table 1).

**EVIDENCE ACQUISITION**

**Search Strategy**

A MEDLINE search was performed of the English-language literature (1966-October 2007) using the MeSH terms neoplasms, germ cell, and embryonal [MAJR] or testicular neoplasms [MAJR] with the subheadings drug therapy, complications, and mortality. To ensure that randomized trials and late relapse reports were not missed, we also performed searches of all randomized trials under the Medical Subject Heading terms neoplasms, germ cell and embryonal or testicular neoplasms and all publications with the words late recurrence or late relapse in association with one of these Medical Subject Heading terms. Articles not pertaining to GCT (ie, gestational trophoblastic neoplasms, ovarian neoplasms, sex-cord stromal tumors) or humans were excluded. In addition, we searched the Cochrane Central Register of Controlled Trials using the terms testicular cancer and germ cell tumors. Bibliographies of review articles and guidelines as well as studies obtained from the search were used to identify additional relevant articles.

**Study Selection**

Of 4389 articles obtained with this search, articles pertaining to tumors metastatic to the testes, localized testicular cancer, phase 1 clinical trials, editorials, commentaries, and review articles (with no original data) were removed. Articles focusing solely on children and women were also removed. In addition, case reports other than those describing chemotherapy-related toxicity or late relapses were excluded. The highest importance was placed on randomized controlled trials and meta-analyses, but phase 2 clinical trials and large retrospective series were also reviewed. For randomized controlled trials, study quality was assessed using the Jadad scale. Additional specific criteria for study selection or exclusion are illustrated in the FIGURE.

**DATA SYNTHESIS**

**Chemotherapy for the Initial Management of Metastatic GCT**

**Good-Prognosis GCT.** The good-prognostic group comprises 60% of patients with metastatic GCT and has a 5-year progression-free and overall survival rate of 88% and 91%, respectively (Table 1). Two chemotherapy regimens are effective for patients with a good GCT prognosis: 4 cycles of etoposide and cisplatin (EP) or 3 cycles of bleomycin, etoposide, and cisplatin (BEP). Randomized trials leading to the establishment of both regimens as standards of care in patients with a good prognosis are summarized in Table 2. These treatment recommendations apply to both seminoma and nonseminoma patients with most randomized trials including both populations. Only 1 published trial and 1 abstract have evaluated advanced seminoma separately from non-
Although results were statistically inferior with EP, the use of only 3 cycles of EP prevented any conclusions regarding the efficacy of standard 4 cycles of EP vs 3 cycles of BEP. The second study demonstrated a superior complete response rate (95% vs 87%) with 4 cycles of BEP compared with 4 cycles of EP, but no improvement in progression-free or overall survival. In addition, the control group underwent 4 (rather than 3) cycles of BEP, and both regimens used an inferior dose of etoposide (360 mg/m²), possibly exaggerating the benefit of incorporating bleomycin into the BEP program. The third trial used an equivalency design to directly compare 4 cycles of EP with 3 cycles of BEP using optimal etoposide doses. There was no difference between the 2 groups in the favorable response rate (complete response + serum tumor-marker-negative partial responses), the study’s primary end point. Progression-free and overall survival also did not differ. Neutropenia was more frequent with 4 cycles of EP, but was counterbalanced by more neuropathy and dermatologic adverse effects with 3 cycles of BEP. The debate continues as to whether either of these regimens is superior to the other. The advantage of the 3 cycles of BEP regimen is the shorter duration of therapy and less cisplatin, while 4 cycles of EP avoids complications associated with bleomycin, including toxic pulmonary effects and Raynaud phenomenon.

Intermediate- and Poor-Prognosis GCT. Patients with metastatic GCT who are less likely to achieve a complete response to chemotherapy can be identified a priori using the International Germ Cell Cancer Collaborative Group risk stratification system. The standard regimen for these patients is 4 cycles of BEP. Attempts to improve outcomes in these subgroups have focused on intensifying the BEP regimen (Table 3), including increasing the cisplatin dose, substituting ifosfamide for bleomycin, using BEP alternating with a second combination regimen, and incorporating high-dose chemotherapy with autologous stem-cell support. These studies failed to demonstrate any advantage over 4 cycles of BEP, and tox-

<table>
<thead>
<tr>
<th>Histology of Germ Cell Tumor</th>
<th>Prognostic Group, %</th>
<th>Prognostic Group, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk-defining features</td>
<td>Good</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Nonseminoma Germ Cell Tumor</td>
<td>All of the following: Primary site not mediastinum; Absence of nonpulmonary visceral metastases; hCG &lt;5000; AFP &lt;1000; LDH &lt;1.5 × ULN</td>
<td>Primary site not mediastinum; Absence of nonpulmonary visceral metastases; And 1 of the following: hCG, 5000-50 000; AFP, 1000-10 000; LDH 1.5-10 × ULN</td>
</tr>
<tr>
<td>Patients</td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>5-y Progression-free survival</td>
<td>89</td>
<td>75</td>
</tr>
<tr>
<td>5-y Overall survival</td>
<td>92</td>
<td>80</td>
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</tbody>
</table>

Seminoma

<table>
<thead>
<tr>
<th>Risk-defining features</th>
<th>Absence of nonpulmonary visceral metastases</th>
<th>Presence of nonpulmonary visceral metastases</th>
<th>Seminomas are never poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma patients</td>
<td>90</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>5-y Progression-free survival</td>
<td>82</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>5-y Overall survival</td>
<td>86</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

| Total With Germ Cell Tumor  | 60                                       | 26                                        |                             |
| 5-y Progression-free survival| 88                                       | 75                                        |                             |
| 5-y Overall survival         | 91                                       | 79                                        |                             |

Abbreviations: AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper limits of normal.
Second- and Third-Line Chemotherapy Regimens

Most patients with testicular cancer who achieve a complete response to initial therapy are cured, with relapses occurring in less than 10% of cases. Patients who relapse after initial chemotherapy can still potentially be cured with second-line and even third-line regimens. Successful approaches consist of either standard doses of 3-drug combinations based on ifosfamide and cisplatin, or alternatively, high-dose chemotherapy with autologous stem-cell support. Durable response rates with conventionally dosed salvage regimens, such as ifosfamide and cisplatin plus either vinblastine or etoposide, range from 7% to 26%. The combination of paclitaxel, ifosfamide, and cisplatin led to a durable complete response in 29 of 46 patients (63%) with a median follow-up of 69 months. The improved outcomes with paclitaxel, ifosfamide, and cisplatin suggest an advantage over ifosfamide and cisplatin plus either vinblastine or etoposide, but may reflect selection criteria. These regimens have only been studied in separate phase 2 trials and have not been compared in a prospective randomized fashion.

Salvage high-dose chemotherapy has been used successfully in patients with GCT since the late 1980s but was initially limited by high rates of treatment-related mortality. Subsequent efforts led to improvements in convenience and efficacy with reduced toxicity. The use of growth factor support and the collection of stem cells from peripheral blood rather than bone marrow represent 2 important strategies.
High-dose chemotherapy treatment includes 2 or 3 cycles of etoposide and carboplatin (with or without cyclophosphamide or ifosfamide). Programs incorporating only 1 high-dose cycle are less effective. Many regimens include 1 or 2 cycles of preparative chemotherapy to facilitate stem-cell mobilization, reduce tumor bulk, and prevent progression prior to high-dose treatment. Several high-dose regimens have been developed but not directly compared. In a large, recently reported series, 63% of 184 patients achieved a durable complete response to high-dose therapy with a median follow-up of 4 years.

Limited data exist to guide the choice of high-dose or conventional-dose chemotherapy for initial salvage treatment. One prospective study found no significant difference in 3-year event-free and overall survival between the 2 approaches. However, the use of only 1 high-dose cycle in this trial limited conclusions because 2 cycles are usually considered necessary to achieve a benefit. In contrast, a retrospective matched-pair analysis of 193 patients treated with either high-dose or conventional-dose chemotherapy in the initial salvage setting estimated a 10% benefit in 2-year disease-free and overall survival with

### Table 2. Randomized Trials of Different First-Line Chemotherapy Regimens in Patients With Good-Prognosis Metastatic Germ Cell Tumors

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Regimens</th>
<th>No. of Cycles</th>
<th>Complete or Favorable Response, %</th>
<th>Durable Response, %</th>
<th>P Value</th>
<th>Superior Regimen</th>
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<tr>
<td>Bosl et al,1988</td>
<td>164</td>
<td>VAB-6</td>
<td>3</td>
<td>96</td>
<td>85</td>
<td></td>
<td>Four cycles of EP has equal efficacy, less toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP</td>
<td>4</td>
<td>93</td>
<td>82</td>
<td></td>
<td></td>
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<td>Einhorn et al,1989</td>
<td>184</td>
<td>BEP</td>
<td>4</td>
<td>97</td>
<td>92</td>
<td>NR</td>
<td>Three cycles of BEP has equal efficacy, less toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEP</td>
<td>3</td>
<td>98</td>
<td>92</td>
<td></td>
<td></td>
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<tr>
<td>Levi et al,1993</td>
<td>218</td>
<td>PV</td>
<td>4</td>
<td>87</td>
<td>84</td>
<td>NR</td>
<td>Four cycles of PVB is more effective</td>
</tr>
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<td></td>
<td></td>
<td>PV</td>
<td>4</td>
<td>82</td>
<td>71</td>
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<td>Bajorin et al,1993</td>
<td>265</td>
<td>EP</td>
<td>4</td>
<td>90</td>
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<td></td>
<td>Four cycles of EP is more effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PV</td>
<td>4</td>
<td>88</td>
<td>76</td>
<td>.02</td>
<td>Three cycles of BEP is more effective</td>
</tr>
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<td>Leorner et al,1995</td>
<td>166</td>
<td>BEP</td>
<td>3</td>
<td>94</td>
<td>86</td>
<td>.01</td>
<td>Three cycles of BEP is more effective</td>
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<tr>
<td></td>
<td></td>
<td>EP</td>
<td>3</td>
<td>88</td>
<td>69</td>
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<td>Bokemeyer et al,1996</td>
<td>54</td>
<td>BEP</td>
<td>3</td>
<td>97</td>
<td>76</td>
<td>.02</td>
<td>Three cycles of BEP is more effective</td>
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<td></td>
<td></td>
<td>BE360C</td>
<td>4</td>
<td>96</td>
<td>56</td>
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<td>de Wit et al,1997</td>
<td>395</td>
<td>BE360P</td>
<td>4</td>
<td>95</td>
<td>91</td>
<td>NR</td>
<td>Four cycles of BE360P is more effective</td>
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<td></td>
<td></td>
<td>E360P</td>
<td>4</td>
<td>87</td>
<td>83</td>
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<td>Horwich et al,1997</td>
<td>598</td>
<td>rdBEP</td>
<td>4</td>
<td>94</td>
<td>91</td>
<td>&lt;.001</td>
<td>Four cycles of rdBEP is more effective</td>
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<td></td>
<td></td>
<td>CEB</td>
<td>4</td>
<td>87</td>
<td>77</td>
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<td>Horwich et al,2000</td>
<td>130</td>
<td>EP</td>
<td>4</td>
<td>95</td>
<td>81</td>
<td>.21</td>
<td>Four cycles of EP remains the standard of care for patients with advanced seminoma</td>
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<td></td>
<td></td>
<td>C</td>
<td>4</td>
<td>92</td>
<td>71</td>
<td></td>
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<tr>
<td>de Wit et al,2001</td>
<td>792</td>
<td>BEP</td>
<td>3</td>
<td>97</td>
<td>89</td>
<td>.02</td>
<td>Three cycles of BEP has equivalent efficacy and toxicity but shorter treatment duration</td>
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<tr>
<td></td>
<td></td>
<td>BEP + EP</td>
<td>3 + 1</td>
<td>97</td>
<td>90</td>
<td></td>
<td></td>
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<tr>
<td>Toner et al,2001</td>
<td>166</td>
<td>BEP</td>
<td>3</td>
<td>88</td>
<td>90</td>
<td>.08</td>
<td>Three cycles of BEP has equal efficacy, less toxicity</td>
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<tr>
<td></td>
<td></td>
<td>rdBEP</td>
<td>4</td>
<td>87</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culine et al,2007</td>
<td>270</td>
<td>BEP</td>
<td>3</td>
<td>95g</td>
<td>91g</td>
<td>.14</td>
<td>Regimens equivalent based on equal efficacy and balanced toxicity</td>
</tr>
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<td></td>
<td></td>
<td>EP</td>
<td>4</td>
<td>97</td>
<td>86</td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: B, bleomycin; C, carboplatin; E, etoposide; E360, 360 mg/m² of etoposide per cycle; NR, not reported; P, cisplatin; rdBEP, reduced-dose BEP (bleomycin, 30 U per cycle; etoposide, 360 mg/m² per cycle; and cisplatin, 100 mg/m² per cycle); VAB-6, vinblastine, actinomycin-D, bleomycin, cisplatin, and cyclophosphamide.

*Three-year failure-free survival.
*Event-free survival.
*Failure-free survival at 1 year (includes partial responses with negative tumor markers).
*This trial included only patients with seminoma. Because the trial closed prematurely, it was underpowered to demonstrate noninferiority of carboplatin so EP remains standard of care. An additional randomized trial performed exclusively in patients with seminoma comparing carboplatin with cisplatin, etoposide, and ifosfamide came to the same conclusion. However, the study was published only in abstract form and therefore is not included in this table and Jadad scoring could not be applied.
*Study used a noninferiority trial design. The significant P value indicates that 3 cycles of BEP are not inferior to 3 cycles of BEP plus 1 cycle of EP resulting in the conclusion that the 2 regimens have equivalent efficacy.
*Progression-free survival (includes partial responses with negative tumor markers).
*Favorable response rate (includes partial responses with negative tumor markers).
high-dose chemotherapy. In the absence of prospective data, investigators have developed prognostic models to predict which patients are likely to achieve a complete response using either strategy. Although the initial salvage treatment approach remains controversial, after 2 or more treatment regimens, high-dose chemotherapy is generally the only curative option.

Alternative options to provide disease control and to palliate symptoms include the combination of gemcitabine plus paclitaxel, gemcitabine plus paclitaxel, and cisplatin plus etoposide. Single-agent options include oral etoposide, doxorubicin, gemcitabine, and paclitaxel. Clinical trials and surgical resection of metastases provide additional treatment possibilities.

**Surgery After Chemotherapy**

Multiple studies have demonstrated the importance of resecting residual masses following first-line or salvage chemotherapy for nonseminoma GCTs. Except in select circumstances, tumor-marker normalization is a prerequisite to postchemotherapy surgery because elevated markers imply residual systemic disease and predict a high likelihood of incomplete resection or recurrence. All sites (retropertitoneal lymph nodes, liver, and lung lesions) should be resected if possible. The incidence of viable GCT (5%-15%) and teratoma (25%-60%) at surgery varies based on pretreatment tumor size, primary tumor histology, and the number of lines of prior therapy. Models to predict the absence of these elements (fibrosis only) have been proposed but are not widely applied due to false-negative rates. The completeness of surgery and histology of resected masses are strong predictors of long-term outcome.

Postchemotherapy surgical resection of seminoma is technically more difficult and carries a higher morbidity due to the desmoplastic reaction frequently induced by treatment. In addition, there is a lower incidence of viable GCT in the surgical specimen and teratoma is not an issue in patients with pure seminoma. Positron emission tomographic scan can be used to guide surgical decisions in this setting.

**Late Relapses**

In the absence of a second testicular primary, most relapses occur within

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**Table 3. Randomized Trials of First-Line Chemotherapy Regimens in Patients With Intermediate- or Poor-Prognosis Metastatic Germ Cell Tumors (GCTs)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Prognostic Group</th>
<th>No. of Patients</th>
<th>Regimens</th>
<th>Complete or Favorable Response, %</th>
<th>Durable Response, %</th>
<th>P Value</th>
<th>Superior Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al., 1987</td>
<td>Poor</td>
<td>72</td>
<td>BEP, PVB</td>
<td>63</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Four cycles of BEP is more effective, less toxic</td>
</tr>
<tr>
<td>Nichols et al., 1991</td>
<td>Poor</td>
<td>153</td>
<td>BEP</td>
<td>73</td>
<td>61</td>
<td>.90</td>
<td>Four cycles of BEP has equal efficacy, less toxicity</td>
</tr>
<tr>
<td>de Wit et al., 1995</td>
<td>Poor</td>
<td>208</td>
<td>BEP</td>
<td>72</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>de Wit et al., 1998</td>
<td>Intermediate</td>
<td>84</td>
<td>BEP</td>
<td>82</td>
<td>79</td>
<td>.72</td>
<td>Four cycles of BEP has equal efficacy, less toxicity</td>
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<tr>
<td>Kaye et al., 1998</td>
<td>Poor</td>
<td>371</td>
<td>BEP + EP, BOP + VIP-B</td>
<td>65</td>
<td>68</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Nichols et al., 1998</td>
<td>Poor</td>
<td>296</td>
<td>BEP</td>
<td>60</td>
<td>65</td>
<td>.29</td>
<td>Four cycles of BEP has equal efficacy, less toxicity</td>
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<tr>
<td>Motzer et al., 2007</td>
<td>Poor</td>
<td>219</td>
<td>BEP</td>
<td>55</td>
<td>48</td>
<td>.53</td>
<td>Four cycles of BEP has equal efficacy, less toxicity</td>
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<tr>
<td>Droz et al., 2007</td>
<td>Intermediate and poor</td>
<td>114</td>
<td>PveBV, H11001</td>
<td>75</td>
<td>54</td>
<td></td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; BEP200, bleomycin, etoposide, and cisplatin (200mg/m² per cycle); BOP, bleomycin, vincristine, and cisplatin; HDCT, 2 cycles of high-dose carboplatin, etoposide, and cyclophosphamide; HDCTb, 2 cycles of high-dose cisplatin, etoposide, and cyclophosphamide; NR, Not reported; PVB, cisplatin, vinblastine, and etoposide; VIP, etoposide, ifosfamide, and cisplatin.

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the first 2 years after completion of treatment; those occurring thereafter are termed late relapses, with an estimated incidence of 2% to 6%. In most reports, the majority of late relapses occur more than 5 years (median, 3-10 years) following the completion of treatment. The latest documented relapse occurred at 32 years. A recent pooled analysis suggested a higher late relapse rate for nonseminoma (3.2%) than seminoma (1.4%). bulky retroperitoneal lymphadenopathy and teratoma in the postchemotherapy retroperitoneal lymph node dissection specimen may also portend a higher risk of late relapse.

Several characteristic features of late relapse are distinct from early relapse and initial disease presentations. These include a preponderance of yolk sac histology and abnormal elevation of AFP compared with hCG. In addition, late relapses are associated with increased chemotherapy resistance compared with early relapse and initial disease. Features associated with improved outcome include localized disease amenable to surgery, teratoma as the sole histology at late relapse, lack of prior chemotherapy, and initial pure seminoma histology.

Because of the generally poor outcome for late-relapse testicular cancer treated with chemotherapy, surgery is the mainstay of management. When primary chemotherapy is applied, paclitaxel-containing regimens are recommended, followed by resection of residual disease. Immunohistochemical and molecular analyses have identified profiles for early and late relapse tumors that may play a role in their contrasting clinical behaviors.

### Acute Toxicities of Chemotherapy

Adverse effects from treatment of GCT separate into early and late events. The commonly used chemotherapeutic agents can all cause myelosuppression leading to febrile neutropenia, bleeding, and anemia. The risk of febrile neutropenia ranges from 5% to 25% with 3 or 4 cycles of BEP or EP. Both growth factor support and prophylactic fluorouracil administration may lower this risk, but neither are used routinely. Myelosuppression and infection are more frequent and severe with high-dose regimens. Adverse effects more specific to each agent are listed in Table 4. Although some adverse effects are reversible, nephrotoxicity, ototoxicity, neuropathy, and infertility may persist in 20% to 40% of patients.

Acute cardiovascular and thromboembolic toxicities have been linked to GCT chemotherapy. Angina pectoris and myocardial infarctions have both occurred during or shortly after cisplatin treatment, possibly due to direct endothelial cell damage or vasospasm, the latter of which could relate to magnesium wasting. Thromboembolic phenomenon including arterial occlusion, deep venous thrombosis, pulmonary emboli, transient ischemic attack, stroke, and retinal artery occlusion, have also been reported with cisplatin treatment.

Acute adverse effects of bleomycin include pulmonary toxicity and Raynaud phenomenon. The incidence of pulmonary toxicity is proportionate to the cumulative bleomycin dose, occurring in 8.5% of patients treated with more than 300 U, and causing death in 1% to 3%. The cumulative bleomycin dose administered during 3 cycles of BEP is 270 U compared with 360 U with 4 cycles. Toxic pulmonary effects may manifest as bronchiolitis obliterans with organizing pneumonia, eosinophilic hypersensitivity, or interstitial pneumonitis. The latter is most common, and carries a risk of progression to pulmonary fibrosis and death, although most cases resolve either autonomously or with administration of corticosteroids.

The incidence of Raynaud phenomenon with bleomycin has been reported to be as high as 37%, occurring most commonly between 4 and 12 months following the completion of chemotherapy. Raynaud phenomenon is characterized by transient vasospasticity of the digital arteries causing pallor or cyanosis from ischemia followed by redness and pain upon reperfusion (hyperemia). In most cases symptoms resolve but may persist in up to 25% of patients 10 to 20 years after treatment. These manifestations are thought to result from direct endothelial cell damage from bleomycin.

### Chronic Toxicities of Treatment

Testicular cancer survivors require more intensive follow-up than their age-matched counterparts because of an elevated risk of serious comorbidities and early mortality. Of patients who survive at least a year from their initial diagnosis, more than 40% of deaths are from nonmalignant causes at a median follow-up of only 10 years. These causes include gastrointestinal disorders (intestinal vascular lesions, hepatobiliary disease, and ulcers), cardiovascular disease, infections, and possibly respiratory illnesses.
dition, these patients are more likely to experience infertility and anxiety than the general population, acute nephrotoxicity, ototoxicity, Raynaud phenomenon, and neuropathy can persist in 20% to 40% of patients. Sarcoidosis is also more common in patients with GCT, although whether this relates to testicular cancer therapy or to an undefined association between the 2 diseases remains unknown.

**Cardiovascular Toxicities**

Several studies have shown an increased risk of cardiovascular events in GCT patients treated with chemotherapy compared with those who did not receive chemotherapy or with healthy age-matched controls. In a series with long-term follow-up, 10% of GCT patients developed either an angina pectoris or myocardial infarction within 20 years after receiving treatment. When other cardiovascular diseases such as heart failure and stroke were included, the incidence rose to more than 18%. Most studies show a 2-fold higher relative risk of such diagnoses compared with the general population. The combination of chemotherapy and radiation appears to predict the greatest risk, especially with radiation to the mediastinum. For myocardial infarctions, the largest difference in risk between testicular cancer survivors and the general population is before the age of 45 years, after which increases in cardiovascular events in the general population narrow this differential. Mortality from cardiovascular causes is also increased for GCT patients.

The primary mechanisms of cardiovascular toxicity may be separated into direct vascular effects of chemotherapeutic agents or indirect effects through induction of cardiovascular risk factors. Direct vascular effects involve damage of endothelial cells, best exemplified by Raynaud phenomenon, which may persist for 20 years after treatment. Raynaud phenomenon has been causally related to bleomycin, but may be exacerbated by cisplatin, vinblastine, or both. Microalbuminuria, a proposed marker of systemic vascular disease reflecting generalized endothelial dysfunction, is also present in up to 22% of long-term testicular cancer survivors treated with cisplatin. This rate is greater than that found in the general population or GCT patients treated only with orchietomy, supporting the direct vascular injury hypothesis. Other markers of endothelial cell activation, injury, or both, including concentrations of von Willebrand factor and plasminogen activating inhibitor 1 (PAI-1) and carotid artery thickness, may also increase with cisplatin therapy and are associated with elevated risks of coronary artery disease and cardiovascular morbidity.

When compared with early stage testicular cancer patients who did not receive chemotherapy or healthy age-matched controls, chemotherapy-treated GCT patients have a significant increase in cardiac risk factors such as hypertension, hyperlipidemia, increased body mass index, renal insufficiency, and metabolic syndrome. Development of some of these comorbidities may relate in part to hormonal changes, such as testosterone deficiency caused by the combination of orchietomy and chemotherapy. The incidence of hyperlipidemia in various studies ranges from 32% to 82%.

**References**

1. References 100, 101, 123, 135, 145-148. Development of some of these comorbidities may relate in part to hormonal changes, such as testosterone deficiency, caused by the combination of orchietomy and chemotherapy. The incidence of hyperlipidemia in various studies ranges from 32% to 82%.

**Metabolic Syndrome**

The metabolic syndrome, a constellation of 3 or more characteristics (abdominal obesity, hypertriglyceridemia, low high-density lipoprotein, hypertension, or insulin resistance) has recently received attention as a risk factor for cardiovascular morbidity and mortality. It may occur in 25% to 40% of testicular cancer survivors compared with only 3% to 4% of the general population.

Other cardiovascular risk factors unrelated to prior testicular cancer treatment, such as smoking and family history, could further increase the likelihood of cardiac events. Randomized studies and guidelines for screening and preventive measures are lacking in this population. However, testicular cancer survivors should be made aware of their increased risk for cardiovascular disease and encouraged to make appropriate lifestyle modifications including adoption of a healthful diet, smoking cessation, and exercising regularly. A detailed history of cardiac risk factors should be obtained and questions about symptoms and events posed on an annual basis. In agreement with others, we also recommend annual evaluation of blood pressure, glucose, and renal function with intervention or referral to the appropriate specialist if abnormalities are detected. In addition, body mass index should be evaluated annually and lipid profiles at least every 5 years (more frequently if another risk factor is present). We recommend early treatment of these conditions, including in patients with borderline values (ie, systolic blood pressure, 130-139 mm Hg) who in other settings are suitable for an observational approach.

There are no data addressing the use of stress testing in this population. Therefore, we suggest decisions regarding stress testing be made on an individual basis, after careful risk factor review, cardiology consultation, and detailed discussion with the patient. Evaluation of testosterone levels could be considered in patients with the metabolic syndrome or hypogonadal complaints and replacement administered. Further studies testing screening and prevention strategies in this population are needed and formal practice guidelines should be developed.

**Fertility in GCT Survivors**

Infertility is a major issue for testicular cancer survivors because of their...
young age at diagnosis, high cure rate, and long life expectancy following treatment. Defined as the inability to conceive a child within a 12-month period of active attempts, infertility is present in 10% to 35% of men156-158 at the time of their testicular cancer diagnosis, with abnormal semen analyses in more than 50%.159-162 The risk of testicular cancer may be as much as 20-fold higher in men with infertility and abnormal semen analyses compared with age-matched controls.163 The link between these 2 diagnoses is only partially explained by common risk factors such as cryptorchidism. Other reasons for pretreatment infertility in testicular cancer patients include hormone production by tumor, anti-sperm antibodies,164-166 contralateral malignancy or in situ carcinoma167 or psychological stress associated with the diagnosis.

Although unilateral orchiectomy does not appear to cause infertility,156 (due to residual adequate spermatogenesis in the remaining testis), primary or postchemotherapy retroperitoneal lymph node dissection may impair fertility due to the potential for interruption of the retroperitoneal sympathetic nerves leading to retrograde ejaculation.168-171 The development of nerve-sparing techniques has dramatically decreased the incidence of this surgical complication compared with the traditional full bilateral retroperitoneal lymph node dissection168,172 and is therefore recommended when appropriate.172,173,174

Nearly 100% of patients become azospermic during and immediately after cisplatin chemotherapy.160,162 Concurrent elevations of follicle-stimulating hormone and luteinizing hormone and decreases in testosterone occur in some patients,100,101,173,174 and persistent increases in follicle-stimulating hormone following treatment may be associated with chronic infertility.173,177 Despite these effects, approximately 50% of patients regain normal sperm counts within 2 years from treatment, and this proportion may increase to as high as 80% within 5 years.160 Pretreatment oligospermia or azospermia predicts a lower likelihood of sperm count recovery following chemotherapy.160,178 Higher doses of cisplatin (more than 4 cycles) are associated with decreased rates of paternity (38% vs 62%)136 and recovery of normospermia160,179 and Leydig cell function.180 Maintenance of antegrade ejaculation after treatment increases the chance of success.156

Paternity rates have increased over the last 20 years because of improved retroperitoneal lymph node dissection technique, reduced treatment intensity, the use of sperm cryopreservation, and novel methods of assisted reproduction.181-184 Up to 50% of testicular cancer survivors who fail to conceive a child naturally may now be able to do so with assisted reproductive techniques.156,158 The current overall rate of successful paternity is estimated to be between 50% and 85%.156-158 Sperm banking prior to the initiation of chemotherapy or retroperitoneal lymph node dissection is recommended because infertility and the desire to father children following treatment cannot be reliably predicted.185 Furthermore, successful paternity and recovery of testosterone levels and fertility are important predictors of quality-of-life outcomes in testicular cancer survivors.175,186 Patients should also be warned about the risk of congenital birth defects with conception during or within 6 months following chemotherapy.187,188 Contraception is strongly encouraged during this time.

Secondary Malignancies

Testicular cancer survivors are at an increased risk of developing secondary malignancies following chemotherapy, radiation, or a combination of these 2 modalities.125,189-193 In a large series comprising more than 40 000 GCT patients from 6 countries with a median follow-up of 11.3 years and more than 2000 patients who were followed up for at least 30 years, nearly 2300 patients (5.6%) developed a secondary solid tumor.194 Compared with the general population, the risk was approximately 2-fold higher with chemotherapy or radiation alone and 3-fold higher with the use of both modalities.194 The absolute risk increased with a longer follow-up time and younger age at initial treatment.191 The highest relative risks were for tumors of the pleura, pancreas, stomach, bladder, and connective tissue, with bladder and stomach cancer accounting for the largest number of excess cases.194 Another recent series estimated the risk of secondary malignancy with either chemotherapy or radiation to approximate that of cigarette smoking.195

Myelodysplastic syndrome and secondary leukemia are also associated with combination chemotherapy for testicular cancer.192,193,196-199 A disproportionate number of these diagnoses has been linked in particular to etoposide, possibly in a dose-dependent fashion.196,199 The relative risk of leukemia within the first 10 years after treatment for testicular cancer ranges from 3% to 7% in various studies.196,197 but returns close to that of the general population after 10 to 20 years.192,196,197,200 A recent study demonstrated that survival rates for GCT patients with secondary malignancies are similar to patients with matched malignancies and no prior cancer history.201

In addition to secondary malignancies, testicular cancer survivors also have an approximate 2% risk of developing a second GCT in the contralateral testicle.202 Patients should be made aware of this risk; regular self-examination and annual physician examination are recommended to screen for such occurrences.

CONCLUSIONS

With overall cure rates of more than 95% (80% for metastatic disease), testicular GCT are considered the model for curable cancer. These favorable outcomes have been achieved through accurate risk stratification system and well-designed sequential clinical trials of risk-tailored chemotherapy. Some patients who are refractory to initial chemotherapy can still be cured with second- or third-line salvage therapy, which includes either ifosfamide-based regimens or high-dose chemo-
therapy with autologous stem-cell support.

Physicians should be aware of the long-term risks in testicular cancer survivors, including infertility, late relapse, secondary malignancies, contralateral testicular cancer, and chronic comorbidities, such as hypertension, hyperlipidemia, heart disease, and the metabolic syndrome. Future research is likely to focus on recognizing and minimizing the late toxicities of therapy, and enhancing the genetic and biologic understanding of GCT to improve on current treatment options.

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