The Management of Advanced Germ Cell Tumors in 2016: The Memorial Sloan Kettering Approach

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In this paper, we review the use of serum tumor markers in risk assignment and response evaluation; the treatment of previously untreated and relapsing patients; the role of surgical resection of residual disease, including retroperitoneal node dissection; and the importance of clinical trials for addressing unanswered questions and testing new therapies.

Introduction

Germ cell tumors are unique among solid neoplasms because cisplatin-based systemic therapy usually eradicates metastatic disease. This ability to cure patients with advanced disease led to evidence-based standards of care, well-defined risk-adjusted treatment algorithms, and the application of both the standards of care and the risk-adjusted algorithms in all disease stages. These achievements have resulted in an increase in the cure rate of metastatic disease from 10% in the 1960s to more than 80% today.[1]

Ninety-five percent of germ cell tumors are testicular primary tumors, but germ cell tumors may also arise in the retroperitoneum, mediastinum, and pineal gland. Retroperitoneal primary germ cell tumors probably arise from an occult testicular germ cell tumor and should be managed as if they were of testicular origin.[2] The incidence of testicular germ cell tumors has risen steadily over the last 20 years and is highest in white and Hispanic men and lowest in Asian and black men.[3] Cryptorchidism predisposes both the affected and unaffected testis.[4,5] Treatment of the undescended testis before puberty decreases the risk of testicular cancer.[6] A family history and certain genetic disorders, such as Klinefelter syndrome and testicular dysgenesis syndrome, also appear to be associated with an increased risk of germ cell tumor.[7,8] Seminoma and nonseminomatous germ cell tumor each comprise approximately 50% of germ cell tumor cases. All medical practitioners should be familiar with germ cell tumors because delays in diagnosis are associated with more extensive disease, more intensive treatment, and reduced cure rates.[9] The management of early-stage (clinical stage IA–IIA, marker-negative) germ cell tumors is based on the histologic type and the American Joint Committee on Cancer stage.[10] Surveillance, surgery, and chemotherapy all have putative roles in achieving cure rates that approach 99% in early-stage disease.

In this review, we discuss the management of patients with previously untreated and relapsing advanced germ cell tumors, the delayed and acute toxicities of systemic treatment, the implications of these toxicities for treatment decision making, surgical resection of residual disease, and potential future directions to improve outcomes. Of note, germ cell tumor trials use specific definitions of response that will be used throughout this paper (Box).

Serum Tumor Markers

Alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (hCG) levels are elevated in 80% of patients with advanced germ cell tumors.[11] AFP production is restricted to nonseminomatous germ cell tumors. Causes of high levels of AFP other than a germ cell tumor include liver damage, hepatocellular carcinoma, other epithelial cancers, and, very rarely, hereditary persistence.[12-14] Increased levels of hCG may be observed in both patients with seminoma and those with nonseminomatous germ cell tumor. Causes of false-positive elevations of hCG include cross-reactivity of the antibody with luteinizing hormone, heterophile antibodies, and treatment-induced hypogonadism. Tumor lysis during the first cycle of chemotherapy may cause abrupt elevations of AFP and/or hCG (“marker surge”), but these do not represent tumor progression.[15] Lactate dehydrogenase (LDH) is elevated in 40% to 60% of men with germ cell...
tumors.[16] Although LDH elevations may be found in many benign and malignant conditions, LDH has independent prognostic value in patients with advanced germ cell tumors. Indeed, disease may be classified as intermediate or poor risk on the basis of the LDH level alone.[1] Serum tumor markers should be measured before and after orchiectomy, with the “S” stage determined using the postorchiectomy marker values obtained closest to the start of chemotherapy.[10]

Response Definitions Unique to Germ Cell Tumor Trials

- **Complete response (CR): must last 4 weeks**
  - CR to chemotherapy: tumor marker and radiographic normalization or marker normalization plus full resection of tumor masses with necrosis and/or teratoma
  - CR to chemotherapy plus surgery: marker normalization + full resection c/w viable germ cell tumor and negative margins
- **Partial response with negative markers (PR−): must last 4 weeks;** tumor marker normalization plus residual mass(es) on imaging but without progression of disease
- **Incomplete response (IR):** anything other than CR or PR−
- **Favorable response (FR):** CR or PR−

Knowledge of the LDH, AFP, and hCG levels immediately prior to chemotherapy is both diagnostic and prognostic and required for the allocation of patients to the proper International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratum (Table 1).[1] Clinical stage I or IIA disease with elevated postorchiectomy levels of AFP and/or hCG is associated with a high likelihood of metastatic disease, and these patients should receive chemotherapy.[17-19] Similarly, increased levels of AFP and/or hCG at the conclusion of chemotherapy usually represent residual viable disease, although exceptions exist.[20] Thus, serial monitoring of AFP and hCG levels is important in patient management. Mazumdar et al analyzed serum tumor marker half-life during the first 2 cycles of chemotherapy and showed that a satisfactory marker decline (< 7 days for AFP or < 3.5 days for hCG) was associated with a better likelihood of complete response (CR) and better event-free survival (EFS) and overall survival (OS) than a slow marker decline (P < .0001).[21] Marker decline, particularly in the poor-risk group, remained a significant prognostic variable after adjustment for IGCCCG risk category (P < .01).[21] Other studies have confirmed these observations, and prospective trials using marker decline as a response criterion are discussed below.

**Initial Chemotherapy for Advanced Germ Cell Tumors**

**Good-risk advanced germ cell tumors**

About 60% of patients with advanced disease have good-risk germ cell tumors.[1] Clinical trials established the curability of metastatic disease with cisplatin-based combination chemotherapy.[22] Subsequent investigations have focused on maintaining efficacy while decreasing toxicity (Table 2). Bleomycin was an early target for toxicity reduction due to its association with pulmonary toxicity, Raynaud phenomenon, and rare treatment-related death. A randomized trial comparing cisplatin, vinblastine, bleomycin, cyclophosphamide, and actinomycin-D (VAB-6) with 4 cycles of etoposide plus cisplatin (EP×4) revealed equivalent CR rates—and EP×4 had less toxicity.[23] Based on these results, EP×4 became the standard treatment for good-risk disease at Memorial Sloan Kettering Cancer Center (MSKCC). Indiana University examined its standard regimen of 4 cycles of BEP (bleomycin, etoposide, cisplatin; BEP×4) in comparison with BEP×3 and showed that the two regimens had equivalent cure rates and minimal pulmonary toxicity.[24] These results established BEP×3 as the standard regimen for good-risk germ cell tumors at Indiana University. Long-term follow-up studies of patients receiving BEP×3 and EP×4, with median follow-ups of 10.1 years and 7.7 years, respectively, showed that the favorable response rates approached 98%, with about 6% of patients relapsing, and 3% to 4% dying of the disease.[25,26] It is now accepted that these two regimens are equivalent in the management of good-risk disease.[22]

Efforts to further reduce toxicity through dose reduction or drug substitution have been unsuccessful. Carboplatin is inferior to cisplatin in EFS, OS, and relapse-free survival.[27-29] A reduction in the cisplatin dose from 120 mg/m$^2$/cycle to 75 mg/m$^2$/cycle led to significantly worse response rates and survival.[30] A reduction of the etoposide dose from 500 mg/m$^2$/cycle to 360 mg/m$^2$/cycle also led to worse OS.[31,32] Therefore, modifications of the recommended dose and schedule of the standard EP×4 and BEP×3 regimens are not routinely indicated. At MSKCC, if the white blood cell count is less than 2.5 × 10$^3$/μL, or the absolute neutrophil count is less than 700/μL on day 22 of the cycle, we delay the cycle for 1 week and have shown that this modification does not
Intermediate- and poor-risk advanced germ cell tumors

BEP×4 is the standard of care for patients with an intermediate- or poor-risk advanced germ cell tumor; durable progression-free survival (PFS) rates are approximately 75% and 50%, respectively. Alternative regimens with equivalent efficacy and less toxicity have not been identified.[35-38] One trial randomized nearly 300 patients to receive either BEP×4 or 4 cycles of etoposide, ifosfamide, and cisplatin (VIP).[38] After a median follow-up of 7.3 years and reclassification by IGCCCG criteria, no statistically significant difference in PFS or OS was observed in intermediate- and poor-risk patients, although VIP did cause greater myelotoxicity.[39,40] Therefore, VIP×4 is an acceptable alternative to BEP×4 if preexisting pulmonary compromise exists.

Recent trials in intermediate- and poor-risk patients have focused on dose intensification and paclitaxel-containing regimens (Table 3). de Wit and Daugaard reported randomized trials in which there were trends toward improved survival.[41,42] A phase III trial comparing BEP×4 vs BEP×2 followed by 2 cycles of high-dose carboplatin, etoposide, and cyclophosphamide with autologous stem cell transplant (ASCT) showed no improvement in CR, PFS, or OS from the addition of high-dose chemotherapy (HDCT).[43] However, in patients with unsatisfactory tumor marker decline, the 1-year durable CR proportion was 61% for those who received HDCT vs 34% for those who received BEP alone (P = .03).[43] These results and others[44-46] laid the groundwork for a phase III trial in which patients with an unsatisfactory tumor marker decline after BEP×1 were randomized to receive either BEP×3 or a dose-dense regimen incorporating paclitaxel, ifosfamide, and oxaliplatin.[47] The 3-year PFS rate was 59% in the dose-dense group vs 48% in the BEP group (P = .05). No difference in grade 1/2 febrile neutropenia or toxic death was observed, more grade 3/4 neurologic and hematologic toxicity occurred in the dose-dense group, and salvage HDCT plus ASCT was required more often in the BEP group. The authors concluded that chemotherapy intensification in response to unsatisfactory tumor marker decline is a promising “personalized” strategy.

The efficacy of paclitaxel, ifosfamide, and cisplatin (TIP) as second-line treatment for patients with relapsed germ cell tumor[48] led to a phase II trial of TIP×4 in 60 patients with intermediate-risk (n = 20) and poor-risk disease (n = 40).[49] A favorable response was observed in 80% of patients, the 3-year PFS rate was 72%, and the estimated 3-year OS rate was 91%.[49] The majority of grade 3 and 4 toxicities were hematologic or electrolyte abnormalities; 18% of all patients experienced neutropenic fever. Levofloxacin prophylaxis reduced the risk of neutropenic fever. A randomized phase II trial of TIP×4 vs BEP×4 in intermediate- and poor-risk patients is now open at MSKCC and several other institutions (ClinicalTrials.gov identifier: NCT01873326). A single-arm study of an accelerated BEP regimen was conducted, and a CR was observed in 17/28 (61%) of intermediate- and poor-risk patients[50]; a randomized trial is ongoing in Australia (ANZCTR12613000496718; ClinicalTrials.gov identifier: NCT02582697).

Toxicity

Acute effects

Pulmonary toxicity, nephrotoxicity, auditory toxicity, peripheral neuropathy, anemia, and febrile neutropenia are well-known potential acute effects of chemotherapy for germ cell tumors. Since BEP×3 and EP×4 are both standards of care,[22] toxicity should be considered in the choice of one regimen over the other in patients with good-risk germ cell tumors. Febrile neutropenia occurs in 5% to 7% of good-risk patients receiving EP×4 or BEP×3,[34] and in 10% to 20% of intermediate- and poor-risk patients receiving BEP×4.[42,51] Compared with other tissues, the skin and lung have a reduced concentration of bleomycin hydrolase, which inactivates bleomycin.[52] Up to 20% of patients who receive bleomycin develop cutaneous flagellate hyperpigmentation.[53,54] The incidence of bleomycin-induced pulmonary toxicity is associated with the cumulative drug dose. After 270 units (the amount given with BEP×3), high-grade lung toxicity is seen in 0% to 2% of patients, while rates range from 6% to 18% after 360 units (the amount given with BEP×4), with
death occurring as a result in 1% to 3%. [40,51,55-59] These differences underscore the importance of correct initial assignment to the appropriate IGCCCG risk stratum to minimize the risk of acute toxicity. Life-threatening lung injury results from interstitial pulmonary fibrosis. [59-61] Bleomycin should be avoided in patients with preexisting pulmonary disease, elite athletes, avid scuba divers, and pilots, in whom even a minor decrease in pulmonary function may have a life-altering impact. [62]

Bleomycin also causes Raynaud phenomenon, characterized by sudden vasoconstriction of the digital arteries in response to cold temperature or stress. Pallor and cyanosis occur at the onset of digital ischemia, followed by redness and pain upon reperfusion (hyperemia). Raynaud phenomenon occurs in 6% to 8% of patients, based on randomized trials. [55,63] In a trial comparing EP×4 vs BEP×4, 8% of patients receiving BEP and no patient receiving EP experienced Raynaud phenomenon. [55] Raynaud phenomenon occurs most commonly between 4 and 12 months after completion of chemotherapy. [64,65] and symptoms may persist for 10 to 20 years after treatment. [64,66] Although Raynaud phenomenon has been classified as a dermatologic toxicity in some trials, [34] its manifestations are thought to result from direct endothelial cell damage.

Less well known are the arterial and venous thromboembolic events that occur as acute side effects of cisplatin-based chemotherapy across a variety of solid tumors. [67,68] The thromboembolic event rate in patients with germ cell tumors who receive cisplatin-based chemotherapy has ranged from 8% to 18%. [67,69,70] A recent study demonstrated that retroperitoneal lymph nodes greater than 5 cm increased the risk of venous thromboembolism, possibly due to disruption of normal venous drainage of the lower extremities. [70] Most venous events are pulmonary emboli. However, arterial events, including angina pectoris, myocardial infarction, and ischemic stroke, have been reported either during or shortly after cisplatin treatment. [67,69,71-76] In the series by Moore et al, arterial events accounted for 11% of all thromboembolic events. [67] Most events occur in the first 2 cycles of therapy, but occasionally later. [67] Therefore, all physicians who care for patients with germ cell tumors must be aware of the acute thromboembolic toxicity linked to cisplatin-based chemotherapy.

**Chronic effects**

Toxicity from germ cell tumor chemotherapy is not only acute but may also be late, permanent, and fatal. Nephrotoxicity, ototoxicity, and neuropathy can persist in 20% to 40% of patients. [77-83] In addition, 20% of patients fail to regain normal spermatogenesis by 5 years after chemotherapy. [84,85] Data have also emerged showing both cardiovascular disease (CVD) and secondary malignancies in long-term survivors.

The evidence for late CVD toxicity after germ cell tumor chemotherapy was recently reviewed, summarizing possible direct effects on the vascular endothelium and indirect effects via the induction of CVD risk factors. [86] The incidence and relative risk of coronary artery disease in patients with germ cell tumors who received chemotherapy, compared with germ cell tumor patients managed with surgery and surveillance alone, ranged from 5.7% to 6.7%, and from 1.35 to 7.1, respectively. [66,87-89] One study showed an increased risk of CVD mortality during the first year after treatment, but had insufficient follow-up to draw conclusions regarding long-term risk. [90] In addition, multiple studies report an association between cisplatin-based chemotherapy and the development of CVD risk factors, including a higher risk of metabolic syndrome. [66,79,87,89,91-94] Patients should be informed of the increased risk for late cardiovascular toxicity and should be encouraged to incorporate lifestyle modifications such as smoking cessation, regular exercise, weight loss, and a heart-healthy diet.

Secondary non-germ cell tumor malignancy has been reported after radiation therapy and/or chemotherapy. [95-98] The overall relative risk of secondary non-germ cell solid tumors in germ cell tumor patients compared with the risk in the general population ranges from 1.4 to 1.9, with the risk increasing 5 years after therapy. [96,99,100] A study of almost 13,000 men treated for nonseminomatous germ cell tumors reported a 40% excess of solid tumors (standardized incidence ratio, 1.43 [95% CI, 1.18-1.73]) after cisplatin-based chemotherapy, whereas no increased incidence of secondary solid tumors followed surgery alone. [98] Secondary myelodysplastic syndrome and leukemia have also been linked to cisplatin and etoposide. [95,101-103] Although the leukemia risk after etoposide seems to be dose-related, there is no apparent safe lower limit, suggesting that patients receiving adjuvant chemotherapy for clinical stage I or II disease need to be informed as well. [101,104]

The risk of both CVD and secondary malignancy is significantly higher when both radiation and chemotherapy are administered than when either modality is used alone. [95,100] Compared with the general population, the risk of developing a solid tumor is twofold higher with chemotherapy or...
radiation alone and threefold higher with the use of both modalities. [95] These risks may figure prominently in the shared decision making in early-stage (I–IIA) disease. Patients with early-stage germ cell tumors should be informed of the high likelihood of being cured with surgery alone (orchiectomy alone followed by surveillance, or retroperitoneal lymph node dissection [RPLND] after orchiectomy when indicated in nonseminomatous germ cell tumor for clinical stage IB disease), especially since curative systemic chemotherapy is available if recurrent disease is detected during surveillance. [100] If radiation is used, the risks of secondary malignant neoplasms and CVD, and the even greater risk if systemic chemotherapy is required for the treatment of relapse, should be discussed. [100]

**Postchemotherapy Surgery**

The role of surgery after cisplatin-based chemotherapy is dependent on the histology, size, and subtype of the tumor. Advanced seminoma is most frequently managed with chemotherapy alone, with surgery reserved for residual masses > 3 cm and increased fluorodeoxyglucose avidity on positron emission tomography (PET) scanning. [105] However, false-positive PET results are now a well-recognized phenomenon, and surgical intervention after primary therapy of seminoma is rarely used today due to the potential for complications. [106] The optimal management of patients with nonseminomatous germ cell tumors, after serum tumor marker levels have normalized, requires both chemotherapy and surgery at all sites of residual disease; no imaging modality, including PET, has been shown to reliably rule out the presence of active disease. [107–112]

Surgery should be considered in all patients with advanced nonseminomatous germ cell tumors whose markers normalize. Except under certain circumstances, [20,113–115] persistent elevation or an increase in the AFP and/or hCG implies residual viable disease and requires treatment with second-line chemotherapy. [116,117] If retroperitoneal disease was present at the start of chemotherapy, RPLND should be considered. RPLND is not necessary in clinical stage III germ cell tumors without retroperitoneal disease before chemotherapy or in clinical stage IS disease, although one study suggests that retroperitoneal disease is more frequent in the latter group than previously thought. [118] The National Comprehensive Cancer Network guidelines and all germ cell tumor experts recommend RPLND after chemotherapy in patients with metastatic nonseminomatous germ cell tumors for any residual retroperitoneal nodes > 1 cm. [119] A bilateral nerve-sparing RPLND is considered the standard operation; infiel relapse is rare when this is performed by an experienced surgeon.

Not all operations called “retroperitoneal lymph node dissection” are the same. In an attempt to minimize the risk of retrograde ejaculation, many modifications have been developed, collectively called “template RPLND.” All template operations have the potential to leave disease behind. In both the primary RPLND (no prior chemotherapy) and postchemotherapy setting, and for both right-sided and left-sided templates, unresected nodes harbor disease of the same histology as the resected nodes between 3% and 25% of the time, putting the patient at risk for late relapse (> 2 years following completion of chemotherapy) and more difficult second operations. Moreover, with a proper bilateral nerve-sparing operation, the incidence of retrograde ejaculation is very low. [120–123]

The management of postchemotherapy residual retroperitoneal masses < 1 cm (defined as a clinical CR) has been debated for decades. [124,125] Two recent studies reported the outcomes of surveillance in mostly good-risk patients who did not undergo RPLND after chemotherapy. [126,127] Neither study reported the number of patients with clinical stage IS or stage III tumors without retroperitoneal disease at presentation. [126,127] In the study by Ehrlich et al, only 26% of patients had a teratoma in the primary site, and in the study by Kollmannsberger et al, median follow-up was only 4.3 years. [126,127] In the combined group of 302 patients from these studies, 15 patients (5%) relapsed in the retroperitoneum. [126,127] The likelihood of relapse and death was statistically greater in patients with intermediate- and poor-risk disease who achieved a clinical CR and were observed. [126] If observation of small residual retroperitoneal masses is chosen as a management policy, it should probably be limited to patients with good-risk nonseminomatous germ cell tumors, given the higher rate of relapse in patients with intermediate- and poor-risk disease. The debate about postchemotherapy RPLND vs surveillance for residual retroperitoneal masses < 1 cm remains unresolved, and two differing philosophies have crystallized. [125] The proponents of surveillance prefer not to subject the majority of patients who will not relapse to the risks of RPLND, accepting the frequency of residual teratoma in unresected retroperitoneal lymph nodes and the infrequent presence of viable residual disease that will require subsequent full-dose salvage.
chemotherapy. At MSKCC, we believe an RPLND is indicated in most of these patients. First, resection of viable disease, should it be present, is treated with 2 more cycles of EP, rather than full-dose salvage chemotherapy at relapse. Second, there is a high likelihood of teratoma at metastatic sites when teratoma is present in the primary tumor, and an occasional teratoma will grow or progress, with somatic malignant transformation, particularly in the setting of late relapse. While uncommon, these events have been associated with fatal consequences that may be prevented. A discussion of these risks during the postchemotherapy treatment planning discussion is essential.

**TO PUT THAT INTO CONTEXT**

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**What Recent Advance Has Improved the Risk Stratification of Patients With Germ Cell Tumors?**

Two studies have confirmed the significance of the degree of tumor marker decline as a prognostic factor, with satisfactory decline being associated with improved event-free and overall survival, as compared with a slow decline in tumor marker levels, which was associated with less favorable outcomes, particularly in patients with poor-risk disease. Thus, tumor marker levels should be regularly monitored in order to help determine the optimal choice of therapy. With regard to treatment choices, 3 cycles of bleomycin, etoposide, and cisplatin (BEP×3) or 4 cycles of etoposide and cisplatin (EP×4) remain the standard of care for good-risk disease, while BEP×4 is the standard for poor-risk disease.

**How Have the Toxicities of Therapy Shaped the Therapeutic Landscape of Germ Cell Tumors?**

The acute and chronic toxicity of chemotherapy must always be kept in mind when making treatment decisions for these patients. Acute and chronic side effects, such as pulmonary toxicity, nephrotoxicity, auditory toxicity, and peripheral neuropathy, are well-known potential adverse effects. Also important, although less-known, are the arterial and venous thromboembolic events that can occur in the first 2 cycles of cisplatin-based chemotherapy. It cannot be overemphasized that the risk of late toxicities, such as secondary malignancies and cardiovascular disease, is significantly higher when both radiation and chemotherapy are administered compared with use of either modality alone.

We always want to avoid bleomycin in patients with renal insufficiency, in heavy smokers, and in men older than 40 years of age. However, in young healthy men we prefer BEP×3 over EP×4 in good-risk disease to reduce the likelihood of platinum-related toxicity. Given the current bleomycin shortage, alternative regimens—EP×4 and 4 cycles of etoposide, ifosfamide, and cisplatin (VIP×4)—are recommended in good- and poor-risk disease, respectively.

**What Questions Still Remain Unanswered?**

What is the best first-line chemotherapy for patients with poor-risk disease and slow marker decline? What is the best salvage chemotherapy regimen—a standard-dose platinum regimen (eg, paclitaxel, ifosfamide, and cisplatin [TIP]) or high-dose chemotherapy? These issues are still unresolved. The TIGER study will hopefully provide an answer to the latter question.

**Salvage Treatment of Relapsed and Progressive Germ Cell Tumors**

Up to 30% of patients with advanced germ cell tumors will either relapse or fail to achieve a CR and will require salvage chemotherapy.[128] A thorough review of this clinical scenario, with an
associated commentary, has recently been published.[129,130] At present, the two major salvage approaches are conventional-dose chemotherapy (CDCT) and HDCT with ASCT (Table 4). CDCT regimens incorporate cisplatin, ifosfamide, and either vinblastine (VeIP) or paclitaxel (TIP). In two series of patients who received initial salvage chemotherapy, the durable CR rate for VeIP was 23%[131] and for TIP it was 63%.[48] As a result, TIP has become the preferred CDCT regimen. Current HDCT regimens can achieve long-term survival in 40% to 60% of patients,[132-135] including 20% to 25% of patients with mediastinal nonseminomatous germ cell tumors, as well as pineal nonseminomatous tumors.[133,136]

CDCT has been tested predominantly in patients who have testis primary tumors and who progress after a favorable response that lasts more than 6 months.[48] HDCT is equally effective, but has greater toxicity that must be considered.[129,130] In contrast to CDCT trials, trials of HDCT have generally been conducted in patients with short-duration favorable responses; late relapses; mediastinal or pineal primary site; or failure of markers to normalize (“incomplete responders”). At MSKCC, 3 cycles of HDCT follow administration of paclitaxel and ifosfamide (the TI-CE regimen), using the “dose-dense” concept that has been shown to be effective in breast cancer.[130,133] Sequential, less intensive HDCT regimens (similar to TI-CE) seem to be less toxic and possibly more effective than single-cycle more intensive regimens.[134] In the only randomized trial to compare CDCT with HDCT, a single cycle of HDCT was administered rather than sequential cycles, 25% of patients assigned to the HDCT arm did not receive HDCT, a 7% treatment-related mortality was observed in the HDCT arm, and patients with incomplete responses to first-line chemotherapy were excluded.[135] The cure of patients with both CDCT and HDCT has resulted in uncertainty regarding the choice and sequencing of CDCT and HDCT, given the varying inclusion and exclusion criteria, the introduction of paclitaxel and ifosfamide into both CDCT and HDCT, and the varying number of HDCT cycles. While retrospective analyses have identified several prognostic factors and a possible benefit from HDCT in some subgroups, the authors concluded that the result “emphasizes the need for another prospective randomized trial comparing CDCT to HDCT in this patient population.”[128,137] These data serve as the foundation for the TIGER trial (ClinicalTrials.gov identifier: NCT02375204), in which patients stratified by risk criteria are randomized to either TIP or TI-CE. This study will test whether CDCT or HDCT is superior as first salvage therapy, and which subgroup(s) require HDCT as first therapy. At MSKCC, the preferred approach for eligible patients requiring salvage therapy is to enroll them in this clinical trial. The trial has been approved by the Alliance and is supported by other US cooperative groups, as well as groups in Europe, Australia, and New Zealand.

Surgery alone may be the correct salvage intervention.[129,130] The majority of late relapses occur after 5 years, and these tumors are more resistant to chemotherapy. Moreover, late relapse, like mediastinal nonseminomatous germ cell tumors, is more likely to undergo somatic malignant transformation.[138] Hence, surgery is essential and may be the only required intervention. Similarly, in rare patients with disease resistant to all chemotherapy but localized to a single site, surgery is the only curative option.

**Personalized Chemotherapy**

The inability to predict resistance is a major barrier to improving outcomes for patients with germ cell tumors. As previously discussed, unfavorable decline in serum tumor marker levels may serve to identify patients who are responding suboptimally and therefore are less likely to be cured. In the study reported by Fizazi et al,[47] patients receiving BEP×4 who had a favorable decline in marker levels after 1 cycle of BEP achieved significantly better PFS (P = .01) and OS (P = .024) than patients with an unfavorable tumor marker decline after 1 cycle of BEP and randomized to receive an additional 3 cycles of BEP.[47] Those randomized to more intensive therapy after the identification of an unfavorable marker decline had an 11% greater PFS, mirroring the results reported by Motzer et al.[43] Hence, trials that incorporate marker decline may facilitate “personalized” therapy for patients with intermediate- and poor-risk disease.

Molecular phenotyping made possible by high-throughput profiling technology may also enable individualized treatment. For example, next-generation sequencing identified an association between cisplatin resistance and mutually exclusive mutations in TP53 and MDM2.[139] This genomic information may eventually be incorporated into the treatment of patients with germ cell tumors, potentially in combination with marker decline rates. The Figure depicts a possible future strategy directed at intermediate- and poor-risk patients, which could drive clinical trials and patient care.
Conclusions

The treatment of patients with advanced germ cell tumors resulted from progress made through clinical trials. Experience matters. Treatment at centers of excellence has been shown to be associated with improved outcomes.[62] The therapy for advanced disease has made possible the surveillance strategies for clinical stage I disease. Evidence suggests that better outcomes are possible in previously untreated intermediate- and poor-risk patients and in those who require salvage chemotherapy. Modern technology now permits genomic tumor evaluation that may allow better subgroup stratification. Although the number of newly diagnosed patients who will eventually die of disease is small, clinical trials of new therapies, including phase II trials of new drugs, remain essential. At MSKCC, BEP×4 is being compared with TIP×4 in previously untreated intermediate- and poor-risk patients (ClinicalTrials.gov identifier: NCT01873326), and the TIGER trial is open for accrual for patients requiring initial salvage. Long-term toxicity is a major issue, since germ cell tumors now account for about 3% to 4% of all cured adult cancer patients.[140,141] Germ cell tumors increasingly represent a paradigm for adult-onset cancer survivorship, and it is important to quantify the prevalence of major CVD risk factors, understand mechanisms of treatment-associated CVD, and ultimately develop and implement prevention strategies and therapeutic interventions. Hence, we are taking part in a comprehensive multi-institutional study to investigate genetic variants associated with the long-term toxicity of platinum-based chemotherapy in germ cell tumors, with an initial focus on ototoxicity and neurotoxicity (National Cancer Institute trial 1R01CA157823-01A1). Participation in these trials is required if progress is to continue.

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Table 4. Selected Experiences of Salvage Therapies for Patients With G...

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