Published in final edited form as:

Curr Opin Oncol. 2017 May ; 29(3): 172–178. doi:10.1097/CCO.0000000000000361.

Recent developments in the management of germ cell tumors

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Abstract

Purpose of review—In the present review, we summarize the recent developments in the management of germ cell tumors (GCTs).

Recent findings—Treatment-related acute and late-onset toxicity remains a key challenge in the management of GCTs. Recent data show that patients with large retroperitoneal lymph node metastases are at increased risk of venous thromboembolism and may benefit from prophylactic anticoagulation. Predictive models have been developed to identify patients with residual retroperitoneal lymph node masses that are more likely to benefit from surgical resection. However, their clinical use remains hampered by relatively low accuracy. There are currently multiple conventional-dose chemotherapy (CDCT) options for salvage therapy in patients with refractory or recurrent disease. In addition, more efficacious high-dose chemotherapy (HDCT) regimens continue to be developed. The role of salvage CDCT versus HDCT is currently being prospectively investigated. Finally, intratumoral heterogeneity is a common finding in cancer and an obvious observation in GCTs. Despite intratumoral heterogeneity, recent studies on nonseminomatous GCT have identified distinct histological subgroups and a potentially lethal clinical phenotype. Importantly, comprehensive molecular profiling so far has not elucidated the biologic basis or the clinical underpinnings of intratumoral heterogeneity in GCTs.

Summary—Remaining challenges to be addressed include minimizing therapeutic toxicity, and improving outcomes in patients with refractory/recurrent GCTs or malignant transformation of teratomas.

Keywords

Germ cell tumors; non-seminomas; seminomas; testicular cancer

INTRODUCTION

In the United States, an estimated 8720 new cases of testicular carcinoma will be diagnosed and only 380 will die of this disease in 2016 [1]. This excellent survival rate was achieved

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through a series of advances in cisplatin-based chemotherapy regimens over the past 50 years [2, 3]. However, for unclear reasons, the incidence of testicular cancer has been steadily increasing in the United States and Europe [4]. Given this rising incidence, and the greater than 35 years-of-life lost per patient [5], it is imperative to elucidate and target the mechanisms of chemotherapy resistance and cancer relapse in the small fraction of patients who succumb to their cancer. Germ cell tumors (GCTs) account for greater than 95% of testicular carcinomas [6]. Furthermore, a small proportion of GCTs originate outside the gonads, mainly in the mediastinum, with an incidence of 1.9–3.4 per 1 million [7]. There is substantial variability in the treatment response of these extragonadal GCTs, and particularly those of mediastinal origin are characterized by inferior clinical outcomes [8]. Therefore, a key remaining challenge is to understand the biologic differences between testicular and extragonadal GCTs, and improve the efficacy of our therapeutic approach.

Given the excellent outcomes in patients with testicular GCTs, particularly those with early-stage disease, the major challenge in these cases is how to reduce treatment-related morbidity without compromising clinical efficacy. In addition, since most patients will survive after a diagnosis of testicular GCT, it is imperative to understand and reduce the long-term risks of therapy. The present review summarizes the most recent advances in the management of GCTs (Table 1).

STRATEGIES TO MINIMIZE TREATMENT-RELATED MORBIDITY

Therapeutic chemotherapy and radiotherapy are recognized risk factors for secondary leukemia, lymphoma, as well as cancers of the bladder, colon, pancreas, kidney, stomach, thyroid, and soft tissue [9–12]. Management decisions should therefore aim to minimize exposure to these treatment modalities without compromising outcomes. In addition, survivors should be regularly monitored for the multiple other potential late-toxicities of GCT therapy such as cardiovascular disease, metabolic syndrome, hypogonadism, osteoporosis, and depression [13–15]. A recent population-based cohort study found that obesity prior to GCT diagnosis is associated with late therapy-related toxicity [16] and therefore these patients may potentially benefit from less intensive treatment modalities, more comprehensive lifestyle modifications, and closer long-term monitoring.

Surgical resection of residual retroperitoneal and/or lung masses is often required in patients with advanced GCTs. Retroperitoneal lymph node dissection (RPLND) of residual masses in patients with non-seminomatous germ cell tumors (NSGCTs) can reveal mature teratomas, necrotic tissue, or residual viable NSGCTs in 40%, 50%, and 10% of cases respectively [17]. Therefore, this potentially very complex and morbid procedure [18] could be avoided in approximately half of these patients if we could predict which residual masses will only contain necrosis [19]. Towards this goal, predictive models have become available [20, 21] but their clinical use remains limited by low accuracy [22], although this may be improved by minor modifications [23]. Furthermore, a recent retrospective analysis suggested that disease recurrence can occur, albeit infrequently, even in cases where only residual fibrosis/necrosis is found following RPLND [24]. Patients who have been heavily pretreated with multiple cycles of chemotherapy that included high-dose chemotherapy followed by

autologous SCT are less likely to harbor necrosis in the RPLND specimens, whereas teratomas or viable cancer can be found in up to 72% of such cases [25].

Retrospective data suggest that patients with large retroperitoneal lymph node metastases (>5 cm in maximal axial diameter) of GCTs are at increased risk of venous thromboembolism (VTE), possibly due to decreased venous drainage [26]. Elevated lactic dehydrogenase (LDH) has also been found to be associated with increased VTE risk [27]. Such patients may benefit from preventive anticoagulation with low-molecular-weight heparin.

Patients with primary mediastinal NSGCTs may be at increased risk for pulmonary complications, particularly in the postoperative setting. For this reason, some experts prefer to treat these patients with VIP (etoposide, ifosfamide, cisplatin) rather than BEP (bleomycin, etoposide, cisplatin) in order to avoid potential bleomycin-induced toxicity [28]. A recent retrospective analysis of patients with primary mediastinal GCTs treated with postchemotherapy surgery at Indiana University suggested that BEP is associated with higher risk for serious pulmonary complications [29]. However, different time frames and patient selection could have biased these results. A cautionary note: if bleomycin-based regimens do provide survival benefit [30–32], avoidance of bleomycin could be a detriment to the care of certain patients with GCTs.

SALVAGE THERAPY FOR REFRACTORY OR RECURRENT GCTs

The optimal salvage strategy for patients with refractory or relapsed GCTs remains to be elucidated. Potential options include second line conventional-dose chemotherapy (CDCT) or high-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (SCT) [33]. Conventional-dose salvage chemotherapy regimens include VIP [34], TIP (paclitaxel, ifosfamide, cisplatin) [35], and VeIP (vinblastine, ifosfamide, cisplatin) [36]. None of these regimens have been compared head-to-head in this setting. However, TIP has emerged as the most commonly used CDCT, in large part because it has demonstrated a 63% durable remission rate [35] compared with 14.6% seen with VIP [34], and 23.7% with VeIP [36], although this difference may be inflated because the TIP trial did not include patients with primary mediastinal NSGCTs or with incomplete response to first-line therapy [35]. Oxaliplatin is a platinum-based chemotherapeutic agent with a different spectrum of antineoplastic activity compared with cisplatin [37]. For this reason, oxaliplatin is often used in patients with GCTs that are refractory to cisplatin-containing regimens. A recent data registry analysis showed that GOP (gemcitabine, oxaliplatin, paclitaxel) with or without additional tumor resection can achieve a complete remission rate of 13.1% when given outside of a clinical trial setting to patients refractory to cisplatin-based chemotherapy who received a median of 3 prior treatments, including HDCT with autologous stem cell transplant in 76% of cases [38].

Autologous SCT allows the administration of chemotherapy combinations at doses that would otherwise be fatal to patients. GCT is a highly chemosensitive malignancy occurring most often in young patients with few comorbidities who can tolerate the toxicities associated with autologous SCT relatively better than other patient populations. HDCT

followed by peripheral-blood autologous SCT can achieve a 2-year progression-free survival of 63% when given as second-line therapy, and 49% when given as third-line or later [39]. The TI-CE regimen consists of paclitaxel and ifosfamide induction for up to 2 cycles followed by high-dose carboplatin and etoposide with autologous SCT every 21–28 days for 3 cycles. The efficacy of this approach was demonstrated in a phase I/II trial that reported a 47% 5-year disease-free survival and 52% overall survival [40]. The TIGER trial (NCT02375204 at www.clinicaltrials.gov) is an ongoing multicenter, open-label phase III study comparing second-line TI-CE vs TIP in patients with relapsed or refractory GCTs. This trial will help determine which patients can benefit more from first salvage therapy with HDCT versus CDCT. Another recent single-arm phase II trial used a rationally designed HDCT combination of bevacizumab, gemcitabine, docetaxel, melphalan, and carboplatin (cycle 1) followed by bevacizumab, ifosfamide, etoposide, and carboplatin (cycle 2) [41]. This strategy exceeded the reported outcomes of prior HDCT regimens, particularly in patients with poor-risk features per the Beyer prognostic model.

INSIGHTS GAINED BY GENOMIC AND HISTOLOGICAL ANALYSES

Although GCTs are currently classified according to their histopathological appearance and anatomical site of origin, more refined taxonomies integrating genomic, epigenomic, transcriptomic, and proteomic data may allow more accurate prognostication and management. Such comprehensive profiling has been undertaken by The Cancer Genome Atlas project (https://cancergenome.nih.gov/) and the results are publicly available for investigators to use in generating or validating hypotheses based on the observed genomic and biological patterns. Whole exome sequencing of testicular GCTs has revealed a relatively low frequency of somatic point mutations (average mutation rate of 0.5–0.9 per Mb) which supports the embryological origin of this malignancy [42–44]. Conversely, chromosome arm-level copy number gains, particularly the presence of an isochromosome of the short arm of chromosome 12 (i12p), are significantly more frequent events [42, 44]. Most GCTs are hyperploid based on cytogenetic studies [45]. The exact role of the genes amplified within i12p remains to be elucidated.

Alterations in *KIT* and *KRAS* genes are the most frequent non-synonymous mutations found in GCTs, suggesting that these oncogenes may play an important role in the pathogenesis and growth of these tumors [42, 43, 46]. Nevertheless, a clinical trial of the KIT inhibitor imatinib did not demonstrate antitumor activity against platinum-refractory GCTs positive for *KIT* expression by immunohistochemistry [47]. It is possible that targeted inhibition of the *KIT* pathway may be necessary but not sufficient on its own to achieve lethality in these tumors. Furthermore, in contrast to imatinib-sensitive malignancies such as gastrointestinal stromal tumors, *KIT* mutations in GCTs are mainly localized on exon 17 and are thus more likely to confer resistance to imatinib [43].

Bagrodia *et al.* [43] showed that 25 of 104 (24%) cisplatin-resistant tumors had genetic defects within the TP53/MDM2 pathway compared with 2 of 76 (2.6%) of the cisplatin sensitive tumors ($P<0.001$). Of note, patients in the cisplatin-resistant cohort had a low death rate (23.1%) and it is unclear whether these patients who succumbed to their disease following salvage platinum-based treatments (such as TIP and high-dose carboplatin) were

the ones who had TP53/MDM2 defects or these alterations only predict resistance to first-line cisplatin-based chemotherapy.

Similarly, Taylor-Weiner *et al.* [44] demonstrated genomic convergence, but did not discern any histological subgroups with prognostic significance, transformation potential, or lethal phenotypes. Because microdissection was not performed, it was unclear whether heterogeneous tumor populations in a mixed GCT (containing embryonal carcinoma, yolk sac tumor, choriocarcinoma, seminoma, and/or teratoma) had disparate mitochondrial priming capabilities [48, 49]. Although the authors showed loss of pluripotent gene expression, NANOG and POU5f1, this would not be unexpected in a differentiated tumor such as teratoma (i.e., GCT evolution). Importantly, intact TP53 and i(12p) were likely to be present in both chemo-sensitive embryonal carcinoma and chemo-resistant teratoma if microdissection had been performed to delineate diverse histological components [50, 51].

GCT is a prototype stem-cell tumor capable of differentiating into multiple lineages and phenotypes. It is an ideal tumor model to test the stem-cell theory of cancer [52] and for the study of intratumoral heterogeneity in which pluripotent cancer cells (e.g., embryonal carcinoma) are intermingled with differentiated cancer cells (e.g., teratoma), and where different tumor components exert or exhibit differential mitochondrial priming despite similar genetic makeup due to a common clonal origin [53]. Tu et al. [54] identified tumor subgroups based on developmental pathways and histological makeups that provided prognostic significance, predicted transformation risk, and revealed lethal phenotypes among GCTs. Their data suggest that embryonic origins may be both biologically and clinically relevant for the purpose of subgrouping GCTs.

NOVEL THERAPEUTIC TARGETS

Therapies targeting immune checkpoint molecules, such as the cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1), have shown excellent efficacy against a variety of malignancies and have thus become powerful new additions to the oncologist's toolbox [55]. PD-L1 is the PD-1 ligand that is often aberrantly expressed on cancer cells resulting in suppression of anti-tumor immunity via the PD-1 signaling pathway. PD-L1 has been found to be expressed in 73–76% of seminonas and 64–89% of NSGCTs at significantly higher levels compared with untransformed testicular tissue [56, 57]. This indicates that agents targeting the PD-1/PD-L1 interaction may be efficacious against GCTs. A recent case report described a patient with advanced embryonal carcinoma who had a rapid clinical response following one dose of first-line nivolumab given erroneously after being misdiagnosed with melanoma [58]. Subsequent analysis of The Cancer Genome Atlas GCT cohort by the authors revealed that almost half of GCT tissues demonstrate evidence of a T-cell-inflamed tumor microenvironment [58]. It is therefore conceivable that therapies targeting the PD-1/PD-L1 pathway may activate and/or attract anti-tumor effector T cells in GCTs. These could be further potentiated by combination with other agents such as anti-CTLA4 antibodies.

The cytokine receptor CD30 is expressed in embryonal carcinomas [59] and some seminomas [60]. Accordingly, 9 patients with CD30-expressing cisplatin-resistant GCTs

were treated with the CD30-targeted monoclonal antibody brentuximab as salvage monotherapy in a small phase II trial [61]. Only 1 patient showed a complete response, another one had a partial response, and 2 achieved stable disease [61]. The tumors quickly developed resistance to therapy, as evidence by increase of serum tumor markers [61]. Therefore, brentuximab is more likely to have a role in CD30-positive GCTs as part of combination regimens rather than monotherapy.

OTHER STRATEGIES TO IMPROVE OUTCOMES

Although GCTs are highly curable tumors in most cases, patients with very poor prognostic features can have 3-year survival rates as low as 6.1% [62]. It is clear that more individualized approaches should be used in these cases. A practical strategy to improve clinical outcome is to identify potentially vulnerable patient subgroups and lethal tumor phenotypes based on pertinent clinical observations and a valid scientific rationale so that an integrated, and perhaps multimodal, targeted approach can be applied in a timely manner. For example, such patients may be predisposed to undergo somatic transformation, and therefore may benefit more from RPLND rather than active surveillance.

For patients whose primary GCTs contain yolk sac tumor and seminoma are at higher risk of developing somatic transformation within their metastatic lesions after chemotherapy, and for death [54]. Of interest, patients whose primary tumors contained the same components along with somatic transformation did not experience a worse outcome [54]. This is consistent with reports indicating that teratomas with malignant transformation confer a much worse prognosis than other GCTs, if surgical resection is not feasible [63, 64].

Similarly, certain patients with clinical stage I GCT whose primary testicular tumor contains yolk sac tumor and seminoma or mixed teratoma (in contrast to pure embryonal carcinoma) may be prime candidates for RPLND, because their residual tumor after chemotherapy tends to contain teratoma and is at increased risk to undergo somatic transformation [54, 65]. These patients may not be ideal candidates for active surveillance, because when they develop recurrent disease they appear to be at higher risk of dying from refractory disease [65]

Therefore, a key to improve outcomes is recognition and awareness of a potentially lethal subgroup of testicular GCT. When an indolent but refractory GCT becomes systemic, the window of opportunity towards a cure may be closed. We propose that early diagnosis and prompt systemic treatment using chemotherapy and localized therapy comprising surgery will improve the clinical outcome and enhance the cure rate of this potentially lethal GCT entity.

CONCLUSION

Significant advances made in the past 50 years have achieved high cure rates even in patients with very advanced germ cell tumors (GCTs). Nevertheless, key remaining challenges include minimizing treatment-related acute and long-term toxicities, optimizing the selection of salvage therapies for refractory or recurrent GCTs, and testing novel agents for the treatment of patients who have progressed on the current standard cytotoxic agents (Table 1).

The current management approaches can impose a substantial burden of unnecessary treatment-related toxicity in some patients who otherwise respond well to therapy, and by the same token can fail others who ultimately succumb to their disease. To address these issues, we must continue to individualize our management decisions, better understand when to deliver new agents, and how to layer in or supplant chemotherapy. Emerging technologies have enabled the comprehensive molecular profiling of GCTs, leading to new biological insights. However, advanced technology, arcane bioinformatics, and intricate experiments will not help us address unsettled questions, devise precise prognostication, and identify plausible therapeutic targets to improve clinical outcomes without the benefit of pertinent clinical observations and the backing of a veritable scientific hypothesis [66, 67].

Acknowledgments

Pavlos Msaouel is supported by the National Institutes of Health T32 CA009666 grant. This work was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant CA016672 (used the Clinical Trials Support Resource)

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KEY POINTS

- Minimizing acute and late-onset toxicity is a key challenge in the management of germ cell tumors.
- The role and optimal timing of high-dose chemotherapy followed by stem-cell transplantation remains to be determined and is currently being prospectively investigated.
- Intratumoral heterogeneity can be traced to developmental pathways and separated by histological subgroups with biologic, prognostic, and therapeutic implications.
- The comprehensive molecular profiling of germ cell tumors may uncover potentially targetable biological pathways and processes.

Table 1

Selected, recently published articles related to germ-cell tumors (GCTs).

First author	Journal Year [Reference]	Highlights
Treatment-related morbidity		
Hauptmann	Br J Cancer 2016 [11]	Increased pancreatic cancer risk after radiation therapy
Hashibe	J Cancer Surviv 2016 [16]	Late therapy-related toxicity: obesity
Dusaud	J Surg Oncol 2016 [19]	Predicting residual masses with only necrosis
Punjani	Can Urol Assoc J 2016 [23]	Predicting residual masses with only necrosis
Mano	J Urol 2016 [24]	Predicting residual masses with only necrosis
Gizzi	Eur J Cancer 2016 [27]	Risk of venous thromboembolism
Ranganath	J Clin Oncol 2016 [29]	Pulmonary complications from bleomycin
Salvage therapy		
Seidel	Urol Oncol 2016 [38]	Gemcitabine, oxaliplatin, paclitaxel: CR 13%
Feldman	Clin Genitourin Cancer 2015 [40]	TI-CE followed by HDCT + SCT
Nieto	Ann Oncol 2015 [41]	Bevacizumab/HDCT + SCT
Giannatempo	J Urol 2016 [64]	Treatment of teratoma with somatic transformation
Adra	J Clin Oncol 2016 [39]	HDCT+SCT experience in a large referral center
Genomic and histological analyses		
Litchfield	Nat Commun 2015 [42]	Mutational spectrum from whole-exome sequencing
Bagrodia	J Clin Oncol 2016 [43]	Cisplatin resistance and TP53/MDM2 defects
Taylor-Weiner	Nature 2016 [44]	Genomic convergence, mitochondrial priming, GCT evolution
Tu	Cancer 2016 [54]	Intratumoral heterogeneity, differentiation, and lethal subtype
Bilen	Oncotarget 2016 [65]	Intratumoral heterogeneity and chemo-resistance
Novel therapeutic targets		
Shah	Cancer Immunol Res 2016 [58]	Case report: anti-PD-1 therapy
Necchi	Clin Genitourin Cancer 2016 [61]	Brentuximab vedotin targeting CD-30 expressing GCTs

Abbreviations: HDCT, high-dose chemotherapy; SCT stem-cell transplantation; CR, complete response.