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State-of-the-Art Management of Germ Cell Tumors

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OVERVIEW

The state of the art management of germ cell tumors (GCT) in 2018 does not include novel agents targeting genomic alterations or exciting immunologic-based approaches but rather the avoidance of pitfalls in everyday practice. The relative rarity of GCT and high curability with correct management create the “perfect storm” for high-stakes errors to occur. This review focuses on several common pitialls that should be avoided in staging and management of early-stage and advanced GCT in order to maximize patient outcomes. A particularly frequent misstep is to base treatment decisions on pre- rather than postorchiectomy tumor markers that, depending on marker directionality, can lead to either undertreatment with potentially inferior outcomes or overtreatment with excess toxicity. Another common mistake is the failure to consider the unique ability of GCT to differentiate and the distinct biology of teratoma (chemoresistance and lack of increased glucose uptake compared with normal tissue), which exerts a pervasive influence on nonseminoma management. This may lead to inappropriate use of PET scan to evaluate the postchemotherapy residual mass and, if negative, the conclusion that surgery is not needed whereas (FDG-negative) teratoma should be removed. It could also result in administration of additional unnecessary chemotherapy to patients with marker normalization but without robust radiographic response after 3 to 4 cycles of BEP. Finally, oncologists should strive to maintain standard chemotherapy doses, not substitute carboplatin for cisplatin, and refer to expert centers when expertise (e.g., RPLND) is not available locally in order to achieve optimal cure rates in advanced disease.

A review of the state of the art in managing germ cell tumors (GCTs) in 2018 differs from that of virtually all other malignancies in which novel therapies releasing checkpoints in the immune system or targeting a mutation integral to the biology of the tumor are leading to unparalleled dramatic improvements in outcome with minute-to-minute change in the standard of care. Nevertheless, GCT enthusiasts can take solace in the fact that despite all of the progress being made in these other malignancies, sensitivity to available therapy and cure rates remain higher in the setting of metastatic GCTs than any other cancer, particularly if treatment is correctly applied.[1,2] The truth is that in GCTs, there has not been as much of a change in treatment options as there has been reinforcement of the knowledge already learned and puffing that knowledge into practice in the management of the disease.

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Despite a lack of new options for managing GCTs, the rarity of the tumor and multifaceted treatment continue to present difficult challenges for the busy oncologist and urologist. There are several nuances that are not easily acquired by treatment of one or two cases per year, and robust surgical experience with GCTs, particularly performance of retroperitoneal lymph node dissections, is limited to only a few centers in each country.[3] Both historic and contemporary data indicate that patients treated at high-volume centers achieve superior outcomes to those treated in the community.[4–6] The following review will focus on the most common pitfalls being made in clinical practice that prevent state-of-the-art management (Table 1).

DIAGNOSIS AND STAGING

A frequent mistake made during the staging of newly diagnosed GCTs is the inability to resist using newer but unnecessary imaging technologies in disease assessment. PET scanning, although useful in staging many malignancies, has essentially no role in the diagnosis or staging of GCTs,[7] even in seminoma. Results may lead to identification of clinically insignificant findings, causing increased patient anxiety and performance of unnecessary diagnostic procedures. Disease sites containing teratoma are nearly always 2-deoxy-2-fluoro-D-glucose (FDG)-negative and yet must be regarded as fully malignant metastases equivalent to other histologies (e.g., yolk sac, choriocarcinoma, etc.) and require systemic chemotherapy.[7] The state of the art is to stick with the basics, which, in most cases, consists of a CT scan of the abdomen and pelvis with contrast, either a chest x-ray or CT of the chest, and the tumor markers human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase. Use of PET scan in GCT management is reserved for evaluation of the large (> 3 cm) residual mass after chemotherapy for seminoma[8] and on an individualized basis in some patients with rising markers without evidence of disease on conventional imaging.

EARLY-STAGE DISEASE

Errors in the management of early-stage disease typically stem from a lack of appreciation of the natural history of GCTs nor the potential for mild imaging or serum tumor marker abnormalities to be unrelated to GCTs. An essential principle to remember is that prognosis and management are dictated by the values of postorchiectomy tumor markers (representing the burden of metastatic disease) in patients with testicular GCT. Making decisions based on pre-orchiectomy marker values can lead to both over- and undertreatment. For example, it is not uncommon for marker levels to normalize following orchiectomy, even when the values were quite elevated preoperatively. In the absence of metastatic disease on imaging, such patients have stage I disease and may not require any further treatment. Treatment of such a patient with full-course chemotherapy for advanced disease will result in unnecessary toxicity and long-term risks. It is important to follow declining marker levels to normalization or rise in such situations and knowledge of the half-lives for AFP (5–7 days) and HCG (1–3 days) can be helpful in predicting the likelihood of normalization.

The potential for false-positive low-level elevation of markers is another important consideration in GCT management. For AFP, the upper limit of normal is often between 6

and 8, but a considerable minority of the population will have an AFP in the 10 to 15 range and, more rarely, between 15 to 25.[9] Heterophile antibodies, insults to the liver (alcohol, viral hepatitis, or hemochromatosis), and hereditary persistence of AFP are additional non-GCT-related etiologies of mildly elevated AFP.[10–12] The marker trend is the key to differentiating such cases from active malignancy. Those that remain stable over several weeks or after cancer- directed intervention such as an orchiectomy are typically not of malignant etiology.

False positives for HCG include testosterone deficiency, marijuana usage,[13] heterophile antibodies,[14,15] and use of some medications. Hypogonadism can cause elevation of HCG via two mechanisms; in less specific assays, increased pituitary secretion of luteinizing hormone secretion in response to low testosterone can cross-react with the assay for HCG due to the substantial homology between luteinizing hormone and HCG.[16] Pituitary secretion of HCG, which can also occur in the setting of hypogonadism, is another potential mechanism of nontumor elevation.[17] The level rarely exceeds 10 ng/mL, and a testosterone suppression test can quickly establish whether hypogonadism is the cause of HCG elevation in suspected cases.[17,18]

Another even more common problem surfaces when practitioners are faced with borderline retroperitoneal lymph nodes in a patient who otherwise would be considered to have stage I disease. There is an approximately 30% likelihood that a retroperitoneal lymph node between 1.0 and 1.5 cm in the testicular tumor landing zone (left para-aortic for left testis tumors and interaortocaval for right testis tumors) will be benign. Nodes outside of the landing zone have even a higher chance of being unrelated to GCTs. As such, borderline lymph nodes can often be followed with a repeat CT scan 6 to 8 weeks later.[19] If the nodes are continuing to enlarge, then they likely represent metastasis, but if they remain stable or are decreasing in size, then they are probably benign. Repeating imaging can avoid overtreatment and does not compromise cure rates in most patients. One must also appreciate that the natural history of GCTs dictates that 90% to 95% of metastatic testicular GCTs will spread to the retroperitoneum first with only 5% to 10% skipping the retroperitoneum and spreading to other sites such as the lungs, mediastinal or neck lymph nodes, or liver. Thus, when approaching a patient with reported skip metastasis and normal tumor markers, one must consider the possibility of nonmalignant etiologies such as sarcoidosis in the case of mediastinal adenopathy and small lung nodules.[20] Biopsy can be helpful in distinguishing these two scenarios.

ADVANCED DISEASE

In patients with advanced GCTs, use of pre-orchiectomy markers for decision-making again emerges as a common mistake. Similar to staging, the postorchiectomy markers must be used to determine International Germ Cell Cancer Collaborative Group prognostic classification that guides chemotherapy selection. It is not uncommon for a patient whose markers are in the intermediate- or poor-risk range pre-orchiectomy to decline to the good-risk range following surgery and would be at risk for increased toxicity if treated as having poor-risk disease. In contrast, a patient with pre-orchiectomy markers in the good-risk range who has a rapid marker rise postorchiectomy to the intermediate- or poor-risk values would

be significantly undertreated with a decreased chance of cure if chemotherapy were selected based on the pre-orchiectomy values.

A final tumor marker consideration is that at the end of chemotherapy, HCG may exhibit a slow terminal decline rather than following the typical 1- to 3-day half-life we see after surgery and the first two cycles. As shown elegantly by Zon et al,[21] patients with prechemotherapy HCG values higher than 50,000 mIU/mL can have a slow decline following completion of their fourth cycle of chemotherapy. More than 50% of men with detectable HCGs that are declining will eventually normalize their HCG values and never require any further chemotherapy.

Another common issue in advanced disease is failure to recognize the importance of teratoma in the postchemotherapy management of nonseminoma. This generally applies to patients who achieve normalization of their markers following chemotherapy but with only a modest decrease in the size of retroperitoneal adenopathy. These patients should not be treated with another two cycles of chemotherapy, given there is no evidence that six cycles is superior to four and that teratoma may explain the lack of radiographic response. Teratoma is not sensitive to chemotherapy such that further chemotherapy is unlikely to garner further reduction in lymphadenopathy and will add toxicity. Instead, surgical resection of the residual nodes should be pursued in this situation. Similarly, PET scan should not be used to evaluate the residual retroperitoneal mass in such cases. Both teratoma and necrosis lack FDG avidity on PET scan, and therefore, a negative PET does not obviate the need for surgical resection.[22] Proceed to surgery and “forget the PET.”

A critically important component of advanced GCT management is to ensure proper chemotherapy dosing to maximize patient outcomes. The standard dose for etoposide is 500 mg/m^2 per cycle and for cisplatin is 100 mg/m^2 per cycle in both the bleomycin, etoposide, and cisplatin and etoposide and carboplatin regimens. Decreasing the doses of either drug has been demonstrated in several studies to lead to inferior outcomes.[23,24] Furthermore, substitution of carboplatin for cisplatin also decreases cure rates and survival.[25–27] In addition to lower cure rates, salvage chemotherapy adds a substantial burden of therapy and toxicity (neuropathy, tinnitus, hearing loss, infertility, secondary malignancies, and cardiovascular disease) such that deviating from standard dosing that maximizes success should be avoided. Patients should also be treated on time every 21 days whenever possible without unnecessary delays.

A final and perhaps the most important pitfall in managing GCTs is not seeking advice or referring to a high-volume center for complicated or unusual cases or when certain expertise is not available at the local treatment site. This applies to most cases in which retroperitoneal lymph node dissection or salvage chemotherapy is required and particularly for patients in whom high-dose chemotherapy with autologous stem cell reinfusion is being considered. Referral to a high-volume center will maximize the chance of cure and limit unnecessary complications and toxicity.

CONCLUSION

Although the state-of-the art management of GCTs may not have changed much over the past decade, it is increasingly recognized how deviations from standard care and failure to refer patients to a high-volume center negatively affect outcome. Simply put, state-of-the-art management of GCTs starts by stating that there is an art to managing GCTs, one that is enhanced by experience in every phase of the disease from surgery to chemotherapy to survivorship.

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PRACTICAL APPLICATIONS

- Measurement of the tumor markers AFP and HCG is an essential component of GCT management. However, it is critical to use the tumor markers obtained after rather than before orchiectomy for staging, estimation of prognosis, and treatment determination as use of pre-orchiectomy markers can lead to either under- or overtreatment.
- Teratoma, a histologic subtype of nonseminoma that represents terminally differentiated somatic tissue, is chemotherapy-resistant and not associated with tumor marker production or FDG-avidity. PET scan cannot differentiate between teratoma and necrosis and has no routine role in nonseminoma management.
- Nonmalignant causes of (low-level) elevation of HCG (hypogonadism, heterophile antibodies) and AFP (alcohol, heterophile antibodies) should be considered before altering management decisions.
- When HCG starts off in the poor-risk range (> 50,000 mIU/mL), it can exhibit a slow terminal decline rate at the end of chemotherapy. A slowly declining HCG may eventually normalize and does not necessarily represent chemotherapy resistance or the need for salvage chemotherapy.
- Randomized trials demonstrate that lowering the doses of cisplatin or etoposide in first-line chemotherapy leads to inferior outcomes as does substituting carboplatin for cisplatin. These practices should be avoided whenever possible.

TABLE 1.

Common Pitfalls in Germ Cell Tumor Management

Disease Setting	Pitfall	Danger
Diagnostic workup	Use of PET scan for staging	Performs no better than CT, yet more expensive and excess radiation exposure; may lead to complacency about FDG-negative masses or overidentification of irrelevant conditions
Early-stage disease	Management based on pre-orchiectomy tumor markers	Can lead to overtreatment of stage I-A or I-B as I-S
	Lack of recognition of causes of false-positive elevations of AFP or HCG	Can lead to overtreatment of stage I-A or I-B as I-S
	Lack of recognition that borderline lymph nodes in the landing zone may be benign	Can lead to overtreatment of stage I as stage II
Advanced disease	Management based on pre-orchiectomy tumor marker levels	Can lead to incorrect IGCCCG classification with potential for over- or undertreatment
	Failure to recognize teratoma as the etiology of lack of shrinkage	Can lead to additional chemotherapy beyond three to four cycles and unnecessary toxicity
	Use of PET in postchemotherapy nonseminoma evaluation	Can lead to omission of surgery predisposing to relapse, particularly late relapse with teratoma or secondary somatic malignancy
	Failure to recognize the slow terminal decline rate of HCG in patients with a high starting HCG value	Can lead to unnecessary use of salvage chemotherapy with considerable toxicity
	Decreasing etoposide or cisplatin doses or substituting carboplatin for cisplatin	Leads to decrease in efficacy (cures and survival)
All phases	Failure to refer patients to expert center (e.g., salvage chemotherapy, need for RPLND, or other complicated situation)	Can lead to a variety of incorrect or insufficient treatments and suboptimal outcome

Abbreviations: GCT, germ cell tumor; FDG, 2-deoxy-2-fluoro--glucose; HCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; IGCCCG, International Germ Cell Cancer Collaborative Group; RPLND, retroperitoneal lymph node dissection.

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