Desperation Postchemotherapy Retroperitoneal Lymph Node Dissection for Metastatic Germ Cell Tumors

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KEYWORDS

• Postchemotherapy • Retroperitoneal lymph node dissection • Germ cell tumors
• Serum tumor markers

KEY POINTS

- Patients with persistently elevated serum tumor markers should be monitored for marker kinetics and evaluated for nonviable cancer causes of marker elevation.
- Desperation postchemotherapy retroperitoneal lymph node dissection is performed in select patients following second-line chemotherapy.
- Adjuvant postoperative chemotherapy is not indicated in patients following second-line chemotherapy.

INTRODUCTION

Patients with advanced germ cell tumors (GCTs) of the testis (cIIB–cIII) and those with persistently elevated serum tumor markers (STM) following radical orchiectomy (cIS) are initially treated with platinum-based chemotherapy according to the International Germ Cell Cancer Collaborative Group risk classification.[1] Approximately 70% to 80% are rendered free of disease following first-line chemotherapy and adjunctive resection of all residual sites of disease.[2] Despite the profound sensitivity of GCTs to platinum-based chemotherapy regimens, approximately 20% to 30% of patients will not achieve undetectable STMs following first-line risk-appropriate chemotherapy or will relapse early following a serologic complete response.[2] With rare exception, these patients are managed with conventional second-line chemotherapy regimens or high-dose chemotherapy with autologous stem cell replacement. With this approach, approximately 50% to 60% of patients will achieve a complete clinical response and long-term freedom from relapse following surgical resection of all sites of residual disease. However, a subset of patients will continue to have persistently elevated STMs and proceed directly to surgical resection, known as a desperation postchemotherapy retroperitoneal lymph node dissection (PC-RPLND), or third-line systemic therapies. In the current article, the indications for and therapeutic outcomes following PC-RPLND and resection of extra-retroperitoneal sites of disease in patients with persistently elevated STMs following chemotherapy are reviewed.

ELEVATED SERUM TUMOR MARKERS FOLLOWING FIRST-LINE CHEMOTHERAPY FOR GERM CELL TUMOR

Although most patients with elevated STMs following first-line chemotherapy for metastatic

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GCT will be managed with second-line chemotherapy, a highly select group of patients will benefit from immediate PC-RPLND. This highly select group represents patients in whom the elevated STMs are associated with nonviable tumor causes of marker elevations (Table 1). Generally, this includes patients who have low-level serum elevations of human chorionic gonadotrophin (b-HCG) or α-fetoprotein (AFP) that are stable and not increasing over time. For patients with a stable but persistently elevated b-HCG following chemotherapy, hypogonadism and test cross-reactivity with luteinizing hormone should be suspected and further evaluated with a testosterone suppression test.[3] In addition, hepatic dysfunction related to hepatitis and alcohol abuse has been shown to be associated with increase serum levels of AFP.[4]

Furthermore, it has been shown that in patients with residual disease consistent with cystic teratoma, these cystic lesions may contain high quantities of AFP or b-HCG that slowly leak back into the serum, leading to low-level elevations of these STMs.[5] In a study from Memorial Sloan-Kettering, select patients with residual retroperitoneal masses that were cystic in nature underwent PC-RPLND. Intraoperatively, the fluid from the cysts was aspirated and analyzed for AFP and b-HCG concentrations. In all cases, the cystic fluid was positive for b-HCG (9/9 cases) or AFP (9/11 cases). Retroperitoneal histology revealed teratomatous elements in all patients and no evidence of viable GCT. Of these patients, 3 patients also had elevated STMs. In 2 patients with elevated serum AFP, both patients had elevated levels of AFP in the cystic fluid and their serum AFP levels returned to normal following surgery. One patient with elevated serum b-HCG had increasing b-HCG levels and progressive disease following RPLND despite having increased b-HCG levels in the cystic mass. This data suggest that carefully selected patients with stable low levels of serum AFP and residual cystic teratomatous disease in the retroperitoneum may benefit from immediate PC-RPLND and avoid second-line chemotherapy.

ELEVATED SERUM TUMOR MARKERS FOLLOWING SECOND-LINE CHEMOTHERAPY FOR GERM CELL TUMOR

In patients undergoing PC-RPLND following second-line chemotherapy in the setting of normal STMs, the rates of viable GCT are approximately 50%.[6,7] However, with improved risk stratification and refinements of second-line chemotherapy regimens, including taxane-based regimens and high-dose chemotherapy, the rate of persistent viable GCT has been declining.[7] Previous studies have demonstrated that although 2 cycles of adjuvant chemotherapy for patients with residual viable GCT following PC-RPLND (normal STMs) after first-line chemotherapy reduces relapse rates, there is no therapeutic benefit for adjuvant chemotherapy after second-line chemotherapy.[8]

For patients with persistently elevated STMs following second-line chemotherapy, the therapeutic options include third-line systemic therapies or, for select patients, PC-RPLND with surgical resection of all residual sites of disease, also known as a desperation RPLND.[2] The selection criteria used to determine acceptable candidates for desperation RPLND highly depends on the individual patient, but ideally these are patients with (1) slowly rising STMs, (2) limited number of residual sites of disease, and (3) disease that is amendable to surgical resection whereby the surgical intent is to cure.

Histologic Findings at the Time of Desperation Retroperitoneal Lymph Node Dissection

The incidence of viable GCT at RPLND in patients undergoing desperation surgery is reported to range between 40% and 80% across several studies (Table 2).[9–11] However, most of these studies include patients undergoing PC-RPLND

Table 1
Cause of elevated serum tumor markers in patients not associated with viable germ cell tumors

Clinical Scenario	Clinical Evaluation
Hypogonadism associated with elevated b-HCG	1. Measurement of serum testosterone 2. Testosterone suppression test
Hepatic dysfunction associated with elevated AFP	1. Measurement of liver function tests 2. Hepatic ultrasound/computed tomographic (CT) imaging 3. Hepatitis panel
Cystic teratoma associated with increased AFP $\pm$ b-HCG	1. CT abdomen/pelvis reveals findings consistent with teratoma 2. STMs remain mildly elevated but stable