Chemotherapy for Good-Risk Nonseminomatous Germ Cell Tumors

Current Concepts and Controversies

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KEYWORDS

• Germ cell tumor • Cisplatin • Bleomycin • Etoposide

KEY POINTS

- Combination chemotherapy results in a high rate of cure for good-risk GCT.
- Surgery is part of the cure process for a significant proportion of patients.
- Three cycles of BEP remains the gold standard, with four cycles of EP an alternative option depending on individual concerns about patient comorbidity and toxicity.
- As data emerge regarding late chemotherapy toxicity, studies of interventions to improve survivorship will be needed.

The rate of diagnosis of germ cell tumors (GCT) has remained fairly constant, and in 2015 it is estimated that 8,430 men will be diagnosed with, and 380 deaths will be attributed to, GCTs.[1] By the International Germ Cell Cancer Consensus Classification, roughly 60% of all metastatic GCTs are classified as good risk.[2] The criteria defining good risk are presented in **Table 1**. This group of patients has an excellent prognosis, with greater than 90% expectation of cure. Treatment standards have not changed much in recent years. This article focuses on key concepts in the development of the currently accepted first-line regimens and addresses some evolving areas of interest, if not controversy.

CONCEPT 1: CISPLATIN COMBINATION CHEMOTHERAPY CAN CURE EVEN ADVANCED GERM CELL PATIENTS

Cisplatin, also known as *cis*-diamminedichloroplatinum, is a platinum alkylating agent that gained considerable attention in testicular cancer because of its significant activity in refractory disease. In 1974, Einhorn and Donohue[3] at Indiana University investigated cisplatin in combination with vinblastine and bleomycin (PVB) with dosing summarized in **Table 2**. A total of 50 patients with disseminated GCT were treated with four cycles of PVB followed by 21 months of maintenance vinblastine, resulting in 74% complete remissions and 26% partial remissions. Five patients with partial remissions were also able achieve disease-free status following surgical resection of residual disease, resulting in an overall 85% disease-free status.

Etoposide, a semisynthetic epipodophyllotoxin derivative, was found to induce complete remissions in patients with cisplatin-refractory GCT,[4–6] leading to study of this active agent in the first-line setting, in combination with cisplatin. From 1981 to 1984 the Southeastern Cancer Study Group and Mid-Atlantic Oncology Program conducted a phase III study to compare PVB with

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Table 1
Criteria defining good-, intermediate-, and poor-risk germ cell tumors

	AFP	HCG	LDH	
Good risk	<1000 ng/ml	<5000 mU/ml	<1.5 × ULN	Gonadal or retroperitoneal primary
Intermediate risk	1000–10,000 ng/ml	5000–50,000 mU/ml	1.5–10.0 × ULN	Gonadal or retroperitoneal primary
Poor risk	≥10,000 ng/ml	≥50,000 mU/ml	≥10 × ULN	Mediastinal primary site; nonpulmonary visceral metastases

Abbreviations: AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Data from International Germ Cell Consensus Classification. A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997;15(2):594–603.

cisplatin, bleomycin, and etoposide (BEP). A total of 261 patients with disseminated GCTs were randomized to four cycles of cisplatin, 20 mg/m^2 intravenous (IV) daily Days 1 to 5; bleomycin, 30 U IV on Days 2, 9, and 16; and either IV vinblastine, 0.15 mg/kg on Days 1 and 2 or IV etoposide, 100 mg/m^2 on Days 1 to 5.[7] Among those receiving BEP, 83% achieved complete remission, compared with 74% of those receiving PVB. Survival was higher among patients on the etoposide arm (P = .048). Both regimens showed similar myelosuppression and pulmonary toxicity, but BEP-treated patients experienced significantly less neuromuscular and gastrointestinal toxicity. As such, four cycles of BEP replaced PVB as the new standard.

It should be noted that resection of residual disease is important toward the cure of GCTs, and often requires coordinated multidisciplinary efforts to achieve optimal outcomes. Incomplete

Table 2
Doses for established chemotherapy regimens for germ cell patients, with a summary of efficacy data

Regimen (Citation)	Agents and Doses	N	Response Rates
PVB × 3 Einhorn & Donohue,[3] 1977	Cisplatin, 20 mg/m^2 Days 1–5 Vinblastine, 0.4 mg/kg Days 1 and 2 Bleomycin, 30 U Days 2, 9, 16 Every 3 wk × 3 cycles	N = 50	CR 85% Durable CR 64%
BEP × 4 Williams et al,[7] 1987	Bleomycin, 30 U Days 2, 9, 16 Etoposide, 100 mg/m^2 Days 1–5 Cisplatin, 20 mg/m^2 Days 1–5 Every 3 wk × 4 cycles	N = 123	CR 83% Durable CR 78%
BEP × 3 Einhorn et al,[11] 1989	Bleomycin, 30 U Days 2, 9, 16 Etoposide, 100 mg/m^2 Days 1–5 Cisplatin, 20 mg/m^2 Days 1–5 Every 3 wk × 3 cycles	N = 88	CR 98% Durable CR 92%
EP × 4 Bosl et al,[17] 1988	Etoposide, 100 mg/m^2 Days 1–5 Cisplatin, 20 mg/m^2 Days 1–5 Every 3 wk × 4 cycles	N = 82	CR 93% Durable CR 82%
BEC × 4 Horwich et al,[37] 2010	Bleomycin, 30 U Day 2 Etoposide, 120 mg/m^2 Days 1–3 Carboplatin, area under the curve 5 Every 3 wk × 4 cycles	N = 260	CR 87% Durable CR 77%
EC × 4 Bajorin et al,[38] 1997	Etoposide, 100 mg/m^2 Days 1–5 Carboplatin, 500 mg/m^2 Days 1 Every 4 wk × 4 cycles	N = 131	CR 88% Durable CR 76%

Abbreviations: BEP, cisplatin, bleomycin, and etoposide; CR, complete remission.