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Genitourinary Cancer

Four Cycles of Etoposide plus Cisplatin for Patients with Good-Risk Advanced Germ Cell Tumors

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Abstract

Background. The National Comprehensive Cancer Network recommends either three cycles of bleomycin, etoposide, and cisplatin or four cycles of etoposide and cisplatin (EPx4) as initial chemotherapy for the treatment of good-risk germ cell tumors (GCTs). To assess the response, toxicity, and survival outcomes of EPx4, we analyzed our experience.

Material and Methods. Response and survival outcomes, selected toxicities, and adherence to chemotherapy dose and schedule were assessed in patients with good-risk GCT who received EPx4 at Memorial Sloan Kettering Cancer Center between 1982 and 2016. The results were compared with our past results and published data.

Results. Between 1982 and 2016, 944 patients with GCT were treated with EPx4, 289 who were previously reported plus 655 treated between January 2000 and August 2016. A favorable response was achieved in 928 of 944 patients (98.3%). Five-year progression-free, disease-specific, and overall survival rates were 93.9%, 98.6%, and 97.9%, respectively. Median follow-up was 7.3 years (range, 2.8 months to 35.5 years). Viable, nonteratomatous malignant GCT was present in 3.5% of 432 postchemotherapy retroperitoneal lymph node dissection specimens from patients with nonseminomatous GCT. Febrile neutropenia and thromboembolic events occurred in 16.0% and 8.9%, respectively, with one treatment-related death. In the more recent 655-patient cohort, full-dose EPx4 was administered to 631 (96.3%), with deviations from planned treatment driven mainly by vascular (n = 13), hematologic (n = 11), renal (n = 7), or infectious (n = 5) events.

Conclusion. EPx4 is highly effective and well tolerated in patients with good-risk GCTs and remains a standard of care. ***The Oncologist*** 2021;26:483–491

Implications for Practice: Four cycles of etoposide and cisplatin (EPx4) is a standard-of-care regimen for all patients with good-risk germ cell tumors with a favorable response rate and disease-specific survival of 98%. Full-dose administration of etoposide and cisplatin and complete resection of residual disease lead to optimal outcomes. EPx4 should be the recommended regimen in active smokers, patients with reduced or borderline kidney function, and patients aged 50 years or older, which are patient groups at increased risk for bleomycin pulmonary toxicity. Because of a risk of acquired severe pulmonary illness, EPx4 may also be favored for patients who vape or use e-cigarettes and during ongoing transmission of severe acute respiratory syndrome coronavirus 2.

Introduction

Most patients with metastatic germ cell tumors (GCTs) are cured with cisplatin-based combination chemotherapy and International Germ Cell Cancer Collaborative Group (IGCCCG) risk-adapted treatment [1]. The good-risk group comprises at least 60% of patients [1–3], and the National Comprehensive Cancer Network (NCCN) recommends

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either four cycles of etoposide and cisplatin (EPx4) or three cycles of bleomycin, etoposide, and cisplatin (BEPx3) as standards of care [4–7].

The EPx4 regimen, developed at Memorial Sloan Kettering Cancer Center (MSK), showed equivalent efficacy and less toxicity than the bleomycin-containing regimen VAB-6 (cisplatin, bleomycin, vinblastine, cyclophosphamide, and actinomycin-D) in a randomized comparison using MSK good-prognosis criteria [8]. BEPx3, developed at Indiana University, showed equivalent efficacy and less toxicity than BEPx4 in a randomized trial of GCT patients with Indiana University favorable-risk features [9]. With median long-term follow-ups of 7.7 years and 10.1 years, respectively, both studies showed nearly identical favorable response, relapse, and overall survival (OS) rates [10, 11].

Only one randomized comparison of EPx4 and BEPx3 has been reported. The Genito-Urinary Group of the French Federation of Cancer Centers (GETUG) conducted an equivalency trial in patients with good-prognosis nonseminomatous germ cell tumors (NSGCTs), defined by the Institut Gustave Roussy prognostic model. No significant difference between EPx4 and BEPx3 was found in the trial's primary endpoint of favorable response rate (97% vs. 95%, respectively; p = .34) [12]. After retrospective IGCCCG risk reassignment and reanalysis, the 4-year event-free survival rate was 91% for BEPx3 and 86% for EPx4 (p = .135), and the 4-year OS was 96% for BEPx3 and 92% for EPx4 (p = .096). Protocol-defined dose reductions and delays occurred in both arms, fewer than 50% of patients underwent postchemotherapy retroperitoneal lymph node dissection (PC-RPLND), incomplete resections were reported, and no correction for multiple testing was performed. Given the limitations of this study and recent editorial commentary [13], we analyzed the efficacy and safety of EPx4 in our large unselected consecutive cohort of patients with metastatic, IGCCCG good-risk GCT.

Material and Methods

This study, approved by MSK's institutional review board, encompassed 944 men with IGCCCG good-risk GCT [1], 289 previously reported [10] plus 655 additional patients treated consecutively between January 1, 2000, and August 15, 2016 (supplemental online Fig. 1). Eligible patients had good-risk disease by IGCCCG criteria or, as established in previous studies, NSGCT classified as intermediate-risk based only on a lactate dehydrogenase (LDH) level of 1.5–3 times the upper limit of normal [14]. All patients received at least one cycle of etoposide and cisplatin (EP) at MSK and were evaluable for response, and none received a third drug (e.g., bleomycin, ifosfamide). All GCT pathology was confirmed at MSK. Implementation of an electronic medical record (EMR) providing improved data availability allowed treatment deviations and selected toxicities to be characterized for the new cohort.

Four cycles of etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 were administered on days 1–5 at 3-week intervals [8, 9]. If the total white blood cell count was <2,500/mm^3 at the start of a cycle, a 7-day delay was permitted [15]. In men aged ≥50 years, granulocyte colony-stimulating factor (G-CSF) support began with cycle 1 [16]. Serum human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and LDH levels were obtained before each cycle. Computed tomography (CT) of the chest and either CT or magnetic resonance imaging of the abdomen and pelvis were performed at baseline and at treatment completion. In patients with NSGCT and normalized AFP and HCG, residual retroperitoneal, pulmonary, and/or nonretroperitoneal nodal masses were resected after chemotherapy. Patients were considered for PC-RPLND if retroperitoneal disease was present at the start of therapy. If viable, nonteratomatous malignant GCT was present in the postchemotherapy specimen, two additional cycles of cisplatin-based chemotherapy were administered.

For the new patient cohort, modern response criteria that included "favorable response" were used [17, 18]. A complete response (CR) to chemotherapy was defined as marker normalization with radiographic disease resolution, or marker normalization plus surgery that revealed necrosis and/or teratoma. A CR to chemotherapy plus surgery was defined as marker normalization and complete surgical resection of viable, nonteratomatous malignant GCT or teratoma with secondary somatic-type malignancy (malignant transformation). A partial response (PR) with negative markers (PR-negative) was defined as marker normalization with residual nonprogressive radiographic abnormalities. Favorable response included both CR and PR-negative, both of which were required to last for at least 4 weeks. Any response other than a CR or PR-negative was deemed an incomplete response (IR).

Survival outcomes were determined for both the combined cohort (n = 944) and the new cohort (n = 655). OS, disease-specific survival (DSS), and progression-free survival (PFS) were defined from the start of chemotherapy and estimated using the Kaplan-Meier method. OS was defined as time to death of any cause, DSS as time to disease-related death, and PFS as time to treatment or disease-related death, IR, or relapse from an initial favorable response. A relapse was defined as disease recurrence after an initial favorable response. For DSS and PFS, deaths from other or unknown causes were censored at time of last follow-up. Second primary GCTs and teratoma-only relapse with negative serum tumor markers were not considered treatment failures. A competing-risk approach was used to evaluate the cumulative incidence of disease-related death (CIDD) and the cumulative incidence of death from other or unknown causes (CIDOC/UC) [19–21]. For DSS, PFS, and CIDD, a complete case analysis was performed to assess whether combining other and unknown deaths affected interpretation of the results.

Febrile neutropenia, thromboembolic events, and deviations from the planned treatment program could be determined from the EMR in the new cohort (n = 655). Dose reduction, dose delay (defined as postponement of any given cycle for >7 days), early treatment discontinuation, or regimen change because of excessive toxicity, and the causes of these deviations, were identified. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

The study cohort consisted of 944 patients with good-risk GCT: 289 previously reported patients [10] with updated follow-up, plus 655 new patients treated between January 1, 2000, and August 15, 2016 (supplemental online Fig. 1). There were no clinically meaningful differences between the baseline characteristics of the previously reported, new, and combined cohorts (Table 1). Outcomes were determined for all patients through September 1, 2018, to allow at least 2 years follow-up.

Treatment Efficacy

A favorable response was achieved in 928 (98.3%) of 944 patients (Table 2). The 5-, 10-, and 20-year OS rates were 97.9% (95% confidence interval [CI]: 96.7%–98.7%), 96.0% (95% CI: 94.0%–97.3%), and 86.0% (95% CI: 79.1%–90.7%), respectively (Fig. 1A). The proportion of favorable responses, incomplete responses, and survival outcomes were similar in the previously reported, new, and combined cohorts (Table 2; supplemental online Fig. 2). The median follow-up time for survivors was 7.3 years (range, 0.23–35.5 years) for the combined cohort and 6.0 years (range, 0.23–17.7 years) for the new cohort. In the combined cohort, 14 deaths from disease occurred at a median of 2.5 years (range, 1.1–15.3 years); one treatment-related death occurred in a patient being treated for bacteremia after cycle 2. Of 928 patients who had a favorable response, 43 relapsed, 37 within 2 years after treatment, four between years 2 and 3, and one each at 8.2 and 9.9 years.

Deaths from other (n = 21) or unknown causes (n = 11) occurred at a median of 10.0 years (range, 1.6–32.1) and 16.1 years (range, 9.5–29.5), respectively; all such patients demonstrated no evidence of disease at last follow-up. All deaths from unknown causes occurred in the previously published 289 patient cohort [10]. The CIDD was 1.7% at 10 years (95% CI: 1.0%–2.8%) and 2.3% (95% CI: 1.2%–4.2%) at 20 years. The CIDOC/UC was 2.3% (95% CI: 1.2%–3.9%) at 10 years and 11.7% (95% CI: 6.8%–18.0%) at 20 years (Fig. 1B). The 5-, 10-, and 20-year DSS rates were 98.6% (95% CI: 97.6%–99.2%), 98.3% (95% CI: 97.1%–99.0%), and 97.6% (95% CI: 95.4%–98.8%), respectively (Fig. 1C). The 5-year PFS rate was 93.9% (95% CI: 92.1%–95.2%), and the 10- and 20-year PFS rates were both 93.3% (95% CI: 91.4%–94.8%) (Fig. 1D). A complete case sensitivity

Table 1. Patient characteristics

Characteristics	Previous cohort (n = 289), n (%) [10]	New cohort (n = 655), n (%)	Combined cohort (n = 944), n (%)
Median age at chemotherapy, years (range)	30 (15–67)	33 (15–77)	31 (15–77)
Median follow-up time, years (range)	15 (0.6–35.5)	6.0 (0.23–17.7)	7.3 (0.23–35.5)
Histology			
Nonseminoma	209 (72.3)	426 (65.0)	635 (67.3)
Seminoma	80 (27.7)	229 (35.0)	309 (32.7)
Primary site			
Testis	277 (95.8)	638 (97.4)	915 (96.9)
Mediastinum[a]	5 (1.7)	15 (2.3)	20 (2.1)
Retroperitoneum	7 (2.4)	2 (0.3)	9 (1.0)
AFP, ng/mL[b]			
Elevated (>15)	96 (33.2)	172 (26.4)	268 (28.5)
Median elevated value (range)	83.3 (15.3–977)	49.1 (15.1–941.5)	59.8 (15.1–977.0)
HCG, U/L[c]			
Elevated (>2.2)	107 (37.0)	346 (53.1)	453 (48.1)
Median elevated value (range)	32 (2.3–4,170)	28.5 (2.3–282,112)	30.0 (2.3–282,112)
LDH, U/L[d]			
Elevated[e]	120 (41.5)	205 (31.6)	325 (34.7)
Median elevated value times ULN (range)	1.29 (1.005–65.0)	1.33 (1.004–29.5)	1.32 (1.004–65.0)
Nonseminoma with LDH elevated, 1.5–3 times ULN[f]	0	30 (7.0)	30 (4.8)

[a]All mediastinal primary tumors were pure seminoma.
[b]Missing for four patients in new cohort.
[c]Missing for three patients in new cohort.
[d]Missing for seven patients in new cohort.
[e]LDH reference range of 60–200 U/L prior to 4/28/2009 and 120–246 U/L thereafter.
[f]Missing for three patients in new cohort.
Abbreviations: AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2. Chemotherapy response

Response	Previous cohort (*n* = 289), *n* (%)[a]	New cohort (*n* = 655), *n* (%)	Combined cohort (*n* = 944), *n* (%)
Favorable response	282 (97.6)[a]	646 (98.6)	928 (98.3)[b]
Complete response	282 (97.6)	515 (78.6)	—
Chemotherapy alone	269 (93.1)	505 (77.1)	—
Chemotherapy + surgery	13 (4.5)[c]	10 (1.5)[d]	23 (2.4)
Partial response with negative markers	—	131 (20.0)[e]	—
Incomplete response	7 (2.4)	9 (1.4)	16 (1.7)

[a]The "favorable response" category was not in use when the previous cohort was reported [10].
[b]Calculated by combining the complete response rate from the previously reported cohort with the favorable response rate from the new cohort.
[c]Of 11 patients with nonseminomatous germ cell tumor (NSGCT), nine had viable, nonteratomatous malignant germ cell tumor at retroperitoneal lymph node dissection (RPLND), one had teratoma with secondary somatic-type malignancy (malignant transformation) at RPLND, and one had viable NSGCT at the time of lung resection. Two patients had seminoma: one with mediastinal seminoma had viable seminoma at the time of mediastinal resection, and one had viable seminoma at the time of RPLND.
[d]Of nine patients with NSGCT, six patients had viable NSGCT at RPLND, one patient had secondary somatic-type malignancy (malignant transformation) at RPLND, one had secondary somatic-type malignancy (malignant transformation) at both RPLND and lung resection, and one had viable NSGCT at lung resection. One patient with seminoma had viable seminoma at RPLND.
[e]Pure seminoma in 115.

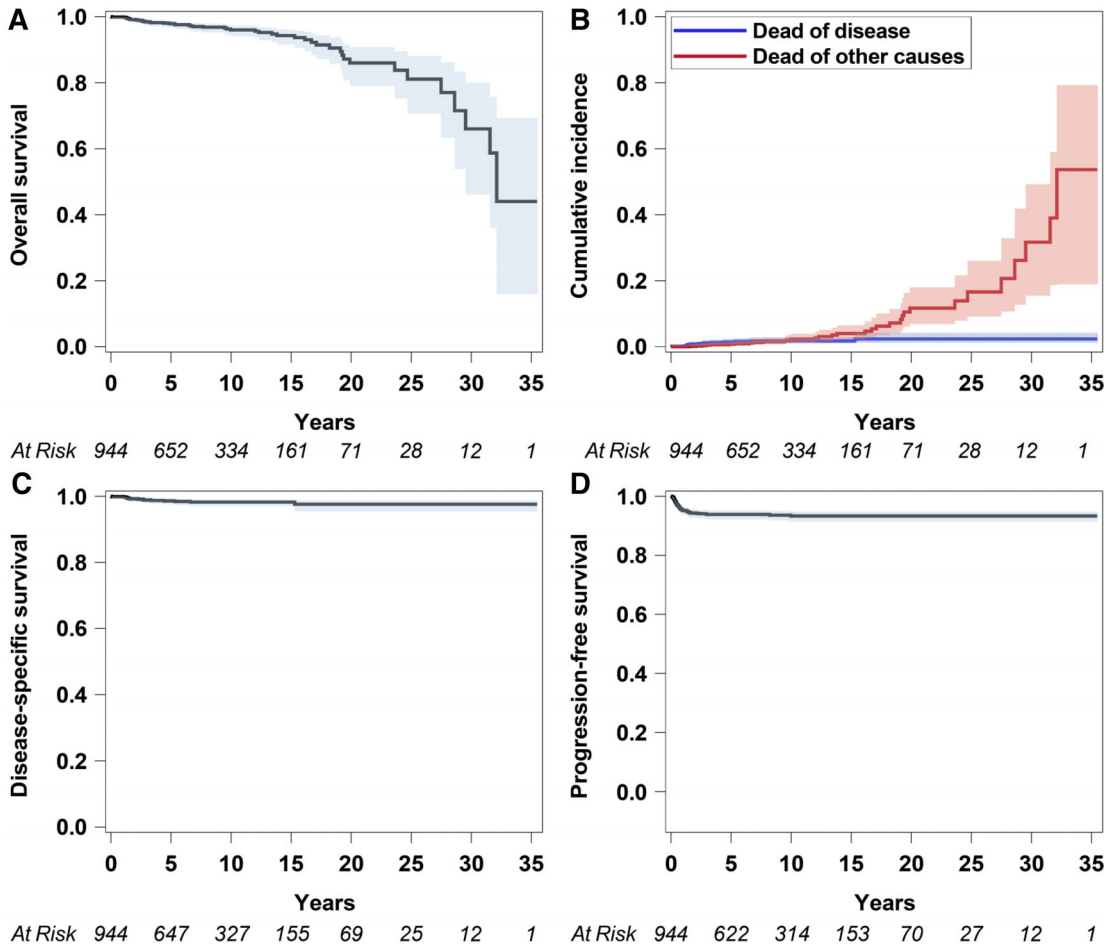

Figure 1. Time-to-event outcomes for the combined patient cohort (*n* = 944). **(A):** Overall survival. Total of 47 deaths; median follow-up for survivors is 7.3 years (range, 2.8 months to 35.5 years). **(B):** Competing risks survival analysis. Event of interest is dead of disease (14 events) or treatment (one event) and competing event is dead of other or unknown causes (32 events). **(C):** Disease-specific survival. Total of 15 disease-related deaths; 32 patients who died of other or unknown causes were censored at time of last follow-up. **(D):** Progression-free survival. Total of 59 events (15 with incomplete response, 43 with relapse and one treatment-related death); 31 patients who died of other or unknown causes were censored at time of last follow-up.

analysis for competing risks, DSS, and PFS that excluded the 11 patients who died of unknown causes yielded similar results.

PC-RPLND for NSGCT

Among 627 patients with NSGCT in the combined cohort who achieved a favorable response, 432 (68.9%) underwent PC-RPLND (Table 3 and supplemental online Table 1). The median time to PC-RPLND from start of chemotherapy was 3.7 months (range, 0.9–9.3 months). The pathologic findings were fibrosis or necrosis in 250 (57.9%) and teratoma with or without fibrosis/necrosis in 167 (38.7%). Three teratomas displayed secondary somatic malignancy. Viable, nonteratomatous malignant GCT was identified in 15 patients (3.5%) [10]. All retroperitoneal lymph node dissection (RPLND) specimens with teratoma or residual viable, nonteratomatous GCT showed negative margins.

PC-RPLND Histology and the Size of Residual Lymphadenopathy

The association between PC-RPLND histology and the size of residual lymphadenopathy on postchemotherapy CT scan was examined in 300 patients with NSGCT from the new cohort with available data. Residual lymphadenopathy was ≥1 cm in 163 (54.3%), and < 1 cm in 137 (45.7%). Teratoma was found in 50.9% (83/163) of specimens with any node ≥1 cm and 24.8% (34/137) with all nodes <1 cm; viable, nonteratomatous malignant GCT was found in 2.5% (4/163) and 1.5% (2/137) of the ≥1 cm and < 1 cm groups, respectively (supplemental online Table 1).

Additional Postchemotherapy Surgery for NSGCT

Additional postchemotherapy surgery was performed in 5.8% (55/944) patients with NSGCT who achieved a favorable response, mostly lung (n = 36) or mediastinal (n = 9) resections. Fibrosis or necrosis was found in 33 (60.0%), teratoma in 18 (32.7%), viable, nonteratomatous malignant GCT in 2 (3.6%), and teratoma with secondary somatic malignancy in one (1.8%); a new primary lung cancer was discovered in one (1.8%). All resections were complete. Summing the RPLND and additional postchemotherapy surgery experience in patients with NSGCT and a favorable response, 21 patients were found to have malignancy other than pure teratoma including 17 with viable GCT, three cases of teratoma with secondary somatic malignancy and one unrelated cancer.

Deviations from the Planned Treatment Program and Toxicity

Full-dose EPx4 was administered to 631 (96.3%) of 655 patients. Six (0.9%) did not complete four cycles of chemotherapy, four (0.6%) had etoposide dose reduction, and 16 (2.4%) had carboplatin substitution for cisplatin after at least one cycle of EP; two patients had two of these reasons for treatment deviation (Table 4). Except for carboplatin substitution, cisplatin dose was not reduced in any patient. Three of four patients who required etoposide dose reduction had human immunodeficiency virus infection, and were being managed with highly active antiretroviral medications, drugs known to modify etoposide metabolism. Dose delays of >7 days occurred in 23 (3.5%) patients, 18 of whom had no other treatment deviation (i.e., otherwise received full-dose EP). The most common treatment-related adverse events leading to treatment deviations were vascular (n = 13), hematologic (n = 11), renal (n = 7), or infectious (n = 5) (Table 5). Febrile neutropenia occurred in 104 patients (16.0%), and 58 (8.9%) experienced a thromboembolic event (Table 4).

Discussion

Among 944 patients treated at MSK with EPx4 for good-risk GCT, a favorable response rate of 98.3%, 5-year OS of 97.9%, 5-year DSS of 98.6%, and 5-year PFS of 93.9% were observed. Fewer than 5% of patients with NSGCT who underwent PC-RPLND had residual viable, nonteratomatous malignant GCT (Table 6). Both the efficacy of EPx4 and its use as a standard of care are confirmed by these results.

EPx4 was also similarly tolerated relative to prior studies [8, 12, 22]. Febrile neutropenia (16%) and thromboembolic

Table 3. Postchemotherapy retroperitoneal lymph node dissection findings in patients with nonseminoma

Finding	Previous cohort, n (%) [10]	New cohort, n (%)	Combined cohort, n (%)
No. of patients with NSGCT and favorable response to EPx4	204[a]	423	627
No. of RPLNDs	127 (62.3)	305 (72.1)	432 (68.9)
PC-RPLND histology category			
Fibrosis or necrotic debris	70 (55.1)	180 (59.0)	250 (57.9)
Teratoma	47 (37.0)	117 (38.4)	164 (37.9)
Teratoma with secondary somatic-type malignancy	1 (0.8)	2 (0.6)	3 (0.7)
Viable, nonteratomatous malignant GCT	9 (7.1)	6 (2.0)	15 (3.5)
Median time from EP start to RPLND, months (range)	3.7 (2.8–6.0)	3.6 (0.9–9.3)[b]	3.7 (0.9–9.3)

[a]The ‘‘favorable response’’ category was not in use when the previous cohort was reported [10].
[b]Four patients had PC-RPLND after 6 months, all delayed for patients’ personal reasons.
Abbreviations: EP, etoposide and cisplatin; EPx4, four cycles of etoposide and cisplatin; GCT, germ cell tumor; NSGCT; nonseminomatous germ cell tumor; PC-RPLND, postchemotherapy retroperitoneal lymph node dissection; RPLND, retroperitoneal lymph node dissection.

Table 4. Chemotherapy treatment and select toxicities (n = 655)

Treatment and toxicity	*n* (%)
Completed full-dose EPx4	631 (96.3)
Completed full-dose EPx4 without delay >1 week[a]	613 (93.6)
Any deviation from planned EPx4[b]	42 (6.4)
Chemotherapy dose delay, >1 week[a]	23 (3.5)
Etoposide dose reduction[c]	4 (0.6)
Cisplatin dose reduction	0 (0)
Cisplatin switched to carboplatin	16 (2.4)
Fewer than four cycles of chemotherapy	6 (0.9)
Febrile neutropenic events[d]	104 (16.0)
Thromboembolic events[e]	58 (8.9)

[a]Eighteen patients had dose delay >1 week and no other deviations and thus received full-dose EPx4; five patients had dose delay >1 week and another deviation and so did not receive full-dose EPx4.
[b]Forty-nine deviations occurred in 42 patients as seven patients had two deviations: four with cisplatin switched to carboplatin and dose delay >1 week; one with cisplatin switched to carboplatin and fewer than four cycles; one with cisplatin switched to carboplatin and an etoposide dose reduction; and one with fewer than four cycles and a dose delay >1 week.
[c]Despite etoposide dose reduction, one of these four patients still received >90% of planned etoposide because dose reduction of etoposide occurred only in cycle 4.
[d]Missing for six patients.
[e]Missing for three patients.
Abbreviation: EPx4, four cycles of etoposide and cisplatin.

Table 5. Causes of deviation from planned four cycles of etoposide and cisplatin (n = 42[a])

Event	*n* (%)[b]
Treatment-related adverse events	
Vascular[c]	13 (31.0)
Hematologic[d]	11 (26.2)
Renal	7 (16.7)
Infectious	5 (11.9)
Hepatic	2 (4.8)
Neurological[e]	2 (4.8)
Taking HAART for HIV	3 (7.1)
Progression of disease	1 (2.4)
Growing teratoma	2 (4.8)
Patient noncompliance	4 (9.5)
Other[f]	2 (4.8)
Unknown	3 (7.1)

[a]Forty-two patients in the new cohort (n = 655) had a deviation from planned four cycles of etoposide and cisplatin (EP).
[b]Nine patients had two reasons and two patients had three reasons for deviation.
[c]Includes both venous and arterial thrombotic events.
[d]Includes cytopenias and febrile neutropenia.
[e]Headache in both patients.
[f]One patient was planned for adjuvant therapy of two cycles of EP but was later noted to have new lymphadenopathy and was therefore treated with another two cycles of EP but with a treatment delay >1 week. A second patient required a hemicolectomy for a newly diagnosed metachronous colon cancer, resulting in a germ cell tumor treatment delay of >1 week.
Abbreviation: HAART, highly active antiretroviral therapy.

events (8.9%) occurred at rates reported in other randomized and retrospective studies [12, 22–26]. Although growth factor prophylaxis is not recommended for most patients [27, 28], we and the NCCN recommend administration of G-CSF to patients above 50 years of age, in whom a 41% rate of neutropenic fever was reported [16]. The NCCN also recommends a bleomycin-free regimen in patients with reduced or borderline kidney function, who are at increased risk for pulmonary toxicity [5, 29]. One undebated advantage of EPx4 is the avoidance of bleomycin-related toxicity, including potential (but rare) pulmonary toxicity. In the GETUG trial, significantly less dermatologic and neurologic toxicity was reported with EPx4 compared with BEPx3 (p < .006); no difference in the frequency of febrile neutropenia was observed [12]. Given emerging reports of pulmonary illness and death related to e-cigarettes and vaping [30–32], a bleomycin-free regimen should be considered in patients who use these products (up to 20.8% of high school students in a recent study [32]). A bleomycin-free regimen may also be favored for patients treated while there is ongoing transmission of severe acute respiratory syndrome coronavirus 2, which can cause pneumonia and hypoxemic respiratory failure [33, 34].

Nevertheless, the efficacy of EPx4 has been questioned by the GETUG trial, an older European Organisation for Research and Treatment of Cancer (EORTC) trial, and a few more recent reports [12, 13, 35–38]. These studies must be interpreted in light of important principles of management of patients with GCT and data analysis. Administration of full *modern* dose etoposide and cisplatin and *complete* resection of residual disease are *required* to achieve optimal GCT outcomes. In the GETUG and EORTC trials, reduced total etoposide and cisplatin dose resulted from either administration of lower dose etoposide as induction therapy, or protocol-defined dose reductions, or both (supplemental online Table 2) [12, 35]. Etoposide and cisplatin dose reduction are both known to result in worse survival in randomized trials [39–41]. In addition, in two of these trials, fewer than 50% of patients who were potential candidates for surgery underwent RPLND, and 6%–12% of patients had an incomplete resection or biopsy of residual disease rather than complete resection (supplemental online Table 2) [12, 35]. The presence of malignant transformation and one new malignancy at postchemotherapy operation in four of 21 patients with NSGCT and residual masses after chemotherapy in our series emphasizes the importance of resection of all disease. Resection of residual retroperitoneal masses <1 cm may be debated, but complete PC-RPLND for masses ≥1 cm and resection of non-retroperitoneal nodal masses and lung nodules are standards of care [42–44].

Importantly, the GETUG trial's conclusions rely on nonsignificant differences after multiple analyses of post hoc endpoints and retrospective IGCCCG risk reassignment [12, 45]. The use of nonsignificant differences to draw conclusions is a known reporting bias that results in misleading recommendations, and multiple post hoc analyses and retrospective risk assignment reduce power and require adjustment [46–48]. Two studies reporting a retrospective analysis of "postchemotherapy surgery" included patients

Table 6. Four cycles of etoposide and cisplatin for metastatic, good-risk GCTs: Summary of the Memorial Sloan Kettering Cancer Center experience

Series	Previous cohort [10], *n* (%)	New cohort, *n* (%)	Combined cohort, *n* (%)
Number of patients	289	655	944
Favorable response	282 (97.6)[a]	646 (98.6)	928 (98.3)[b]
Viable, malignant nonteratomatous GCT at PC-RPLND[c]	9/127 (7.1)	6/305 (2.0)	15/432 (3.5)
Number of relapses, 5-year rate[d]	18 (5.7)[e]	25 (3.9)	43 (4.5)
Number died of GCT, 5-year rate[f]	11 (2.9)[e,g]	4 (0.7)	15 (1.7)

[a]The prior publication did not report a "favorable response" rate, so this denotes the complete response rate [10].
[b]Calculated by combining the complete response rate from the previously reported cohort with the favorable response rate from the new cohort.
[c]For patients with nonseminoma and favorable response to four cycles of etoposide and cisplatin.
[d]Five-year Kaplan-Meier estimate and defined as relapse after an initial favorable response. All relapses occurred within 5 years, except for two in the previous cohort (occurring at 8.2 and 9.9 years).
[e]One patient relapsed and died of disease after publication of the previously reported cohort, which initially reported 17 relapses and nine deaths from disease.
[f]Five-year cumulative incidence estimate of disease-related death.
[g]One treatment-related death that was previously counted as a death from other causes in the previous cohort is now counted as a death from GCT.
Abbreviations: GCT, germ cell tumor; PC-RPLND, postchemotherapy retroperitoneal lymph node dissection.

referred at the time of disease progression. This selection bias led to an increase in the proportion of patients with viable residual disease after EPx4 compared with BEPx3 [37, 38]. However, "postchemotherapy surgery" should be limited to patients referred after completion of chemotherapy and not include those in whom surveillance was chosen and who were referred for surgery only after progression of disease. In a separate study conducted at MSK that excluded postchemotherapy operations at the time of relapse, the rates of viable, nonteratomatous malignant GCT after EPx4 and BEPx3 were 6.1% and 5.4%, respectively [49]. Missing data in known and unknown covariates, such as the number of nodes, the RPLND template, treating institution, patient age, marker levels, primary tumor histology and small sample event size limit the value of methods used to address selection bias (e.g., propensity scoring) and may amplify the biases that they are intended to minimize [50–57].

This study has limitations. First, it is a retrospective, single-center study. However, MSK is a high-volume GCT treatment center and adherence to drug dose and schedule and standard surgical principles are consistent, minimizing selection bias and permitting our accounting of clinical outcomes, treatment modifications, and postchemotherapy surgical findings. Furthermore, most patients live within the catchment area (about 50 miles) of MSK and the proportion of good-, intermediate-, and poor-risk patients is similar to that of the IGCCCG, indicating little referral bias. Second, data were not systematically collected on cardiovascular disease and secondary non-GCT malignancies in long-term survivors. These factors likely account for the small number of deaths from unknown causes in patients who were free of disease but lost to long-term follow-up. We accounted for these deaths, as we have done previously, by using a competing risks approach to separate CIDD from CIDOC/UC. As we have previously shown, a wide temporal disassociation exists between CIDD and CIDOC/UC, with a short interval from diagnosis to death due to disease and a much longer interval from diagnosis to death due to other causes during long-term follow-up. As such, late deaths of unknown cause are highly unlikely to be due to disease [21].

Conclusion

EPx4 is highly effective and well tolerated and remains a standard of care for patients with good-risk GCT. A properly powered randomized trial comparing the efficacy and toxicity of BEPx3 and EPx4 will likely never be conducted, as the sample size would be prohibitively large. Adherence to dose and schedule guidelines and complete resection of residual disease are the two management principles essential to achieve optimal outcomes, with rare exceptions driven by excessive toxicity, drug-drug interactions, or severe comorbidity. Management collaboration with high-volume centers is encouraged, particularly for RPLND, because this procedure is not well represented during training and requires an experienced surgeon [58–61]. Future efforts should focus on maintaining or improving efficacy, decreasing acute and chronic toxicity, and monitoring survivors for late cardiovascular effects and second non-GCT malignancy.

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Disclosures

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