Early experience with chemotherapy intensification for poor-prognosis metastatic germ cell cancer and unfavorable tumor marker decline

Anupam Batra, MD[1]; Scott Ernst, MD[1]; Kylea Potvin, MD[1]; Ricardo Fernandes, MD[1]; Nicholas Power, MD[2]; James Vanhie, MSc[3]; Eric Winquist, MD[1]

[1]Division of Medical Oncology, Department of Oncology, Western University and London Health Sciences Centre, London, ON, Canada; [2]Division of Urology, Department of Surgery, Western University and London Health Sciences Centre, London, ON, Canada; [3]London Health Sciences Centre, London, ON, Canada

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Abstract

Introduction: Intensified chemotherapy improved outcomes for men with poor-prognosis metastatic germ cell cancer (GCC) and unfavorable tumor marker decline after one cycle of bleomycin, etoposide, and cisplatin (BEP) chemotherapy in the GETUG-13 trial. Herein, we report our experience to date using a similar approach.

Methods: Patients were identified from our electronic GCC database. Men with poor-prognosis GCC and unfavorable tumor marker decline were offered intensified chemotherapy consisting of T-BEP (three cycles) plus paclitaxel, ifosfamide, and cisplatin (TIP) (one cycle), along with prophylactic granulocyte-colony stimulating factor (G-CSF) and resection of residual masses. Cisplatin, etoposide, and ifosfamide (PEI) replaced the last cycle of T-BEP for bleomycin pulmonary concerns. Serious toxicities, progression-free survival, and overall survival were evaluated retrospectively.

Results: Ten patients with poor-prognosis GCC were identified from May 2012 to April 2016. Eight patients had unfavorable tumor marker decline. Six were offered and received intensified chemotherapy (two T-BEPx3 + TIP and four T-BEPx2 + PEI + TIP). Serious toxicities included neutropenic sepsis, deep venous thrombosis, and *C. difficile* colitis, but there were no toxic deaths. One patient died of synchronous metastatic adenocarcinoma ex teratoma. The remaining five patients achieved marker-negative partial response, two had residual mature teratoma excised, and four have no evidence of disease after surgery. All are alive at a median of 63.5 months (range 46.3-65.6); one patient has grade 2 peripheral sensory neuropathy, and one patient has grade 2 cognitive disturbance. Of four patients treated with standard BEP, two have died of disease and two are alive at 51.4 and 53.6 months.

Conclusions: Our experience with intensified chemotherapy for men with poor-prognosis GCC and unfavorable tumor marker decline confirms that it is feasible, reasonably safe, and appears to provide results similar to those reported in GETUG-13.

Introduction

Men with metastatic germ cell cancer (GCC) are classified for treatment according to the International Germ Cell Consensus Classification (IGCCC) prognostic classification.[1] Of men with newly diagnosed non-seminomatous GCC, 56% have good-prognosis disease, 28% have intermediate-prognosis disease, and 16% have poor-prognosis disease; five-year survivals are 92%, 80%, and 50%, respectively. Four cycles of either bleomycin, etoposide, and cisplatin (BEP) or etoposide, ifosfamide, and cisplatin (VIP) chemotherapy remain the standard treatment for patients with poor-prognosis GCC.[2,3] Considerable effort has been devoted to improving on the results of BEP in these patients by adding new agents or dose-intensification, including high-dose chemotherapy (HDCT) with stem cell support.[4] However, randomized trials studying these approaches in unselected patients over the past 25 years have been negative.[5]

In 2004, Fizazi and colleagues reported that patients with poor-prognosis GCC and favorable tumor marker decline three weeks after the first cycle of BEP had better four-year progression-free (64% vs. 38%) and overall (83% vs. 58%) survival compared to patients with unfavorable marker decline.[6] These data provided the rationale for the only positive randomized trial in poor-prognosis GCC reported to date. GETUG-13 assessed the efficacy of intensified chemotherapy in men with poor-prognosis GCC and unfavorable tumor marker decline after one cycle of standard BEP.[7] Men were randomly assigned to receive either three more cycles of BEP or an intensified chemotherapy regimen consisting of intravenous paclitaxel-BEP (T-BEP) for two cycles followed by cisplatin, infusional bleomycin, and ifosfamide (PBI) for two cycles, along with doses of oxaliplatin given on day 10 of each cycle. Primary prophylaxis with granulocyte-

colony stimulating factor (G-CSF) was given each cycle. A total of 254 patients were enrolled and evaluable for tumor marker decline, and 203 (80%) had unfavorable tumor marker decline and were randomized. The results validated first-cycle tumor marker decline as a prognostic factor in this population, and provided proof-of-principle for the benefits of chemotherapy dose intensification: three-year progression-free survival (PFS) (59% vs. 48%; hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.44–1.00; p=0·05) and overall survival (OS) (73% vs. 65%; HR 0.78; 95% CI 0.46–1.31; p=0.34) were improved, and the need for subsequent salvage HDCT was reduced with intensified chemotherapy compared to the BEP control arm (6% vs. 16%). As expected, more frequent neurological and hematological toxicity was seen with intensified chemotherapy but there was no increase in toxic death.

Although most expert clinicians agree it should be offered to selected patients, consensus is incomplete about use of intensified chemotherapy in this population and it has not been widely adopted.[2] The main points of controversy relate to the components and schedule of the intensified chemotherapy regimen used in GETUG-13, which consisted of a total of four additional 21-day cycles of chemotherapy following cycle 1 BEP: cycles 2 and 3 were T-BEP-O (BEP plus paclitaxel 175 mg/m^2 IV over three hours day 1 and oxaliplatin 130 mg/m^2 IV day 10), and cycles 4 and 5 were PBI (cisplatin 100 mg/m^2 IV over two hours day 1, bleomycin 25 units daily by continuous IV infusion over 24 hours for five days day 10-14, and ifosfamide 2 mg/m^2 IV over three hours days 10, 12, and 14). Oxaliplatin had initially been included in cycles 4 and 5; however, it was omitted after 12 patients were treated due to excessive peripheral neuropathy; 89% (93/105) of patients received PBI alone.

A first concern is that this regimen was not developed using a conventional phase 1–2 approach and required post-hoc modification for safety. Second, although the rationale for addition of oxaliplatin as a first-line agent is apparent from its activity in the palliative treatment of refractory GCC, there is no evidence that adding it to first-line cisplatin-based therapy is beneficial.[8] This is not the case for paclitaxel, which appeared to improve outcomes when added to BEP.[9] Third are safety concerns of giving bleomycin beyond 360 units, along with recent evidence that continuous infusion does not reduce pulmonary toxicity, and little evidence for incremental benefit with greater cumulative bleomycin dose.[10] Finally, the rationale for the unconventional administration schedules of cisplatin and ifosfamide in cycles 4 and 5 was unclear, and cisplatin given as a single, high dose likely increases toxicity.

In view of these concerns and in the absence of regulatory or funding approval for oxaliplatin for this indication, we began offering chemotherapy intensification with a modified regimen based on the GETUG-13 schedule (see Methods) to men with poor prognosis GCC and unfavorable tumor marker decline at our institution and report our results to date.

Methods

Eligible men with IGCCC poor-prognosis GCC were treated at London Health Sciences Centre between May 2012 and April 2016. Patients were identified from our electronic GCC patient database and had evidence of testicular, retroperitoneal, or mediastinal GCC. Patients with poor-prognosis disease had very elevated tumor markers (serum alfa-fetoprotein [AFP] >10 000 µg/L; serum human chorionic gonadotropin [HCG] >50 000 IU/L; or serum lactate dehydrogenase [LDH] >10 times the upper limit of the normal range), primary mediastinal non-seminoma, or non-pulmonary visceral metastases. Predicted time to normalization of tumor markers was calculated from baseline and day 22 AFP and/or HCG values as previously described.[6] Patients with a rise in tumor marker at day 22 or time to normalization of tumor markers greater than nine weeks for AFP or six weeks for HCG after cycle 1 BEP or VIP were classified as having unfavorable tumor marker decline and offered chemotherapy intensification starting at cycle 2.

Intensified chemotherapy consisted of T-BEP for cycles 2, 3, and 4 followed by one cycle of TIP (paclitaxel 250 mg/m^2 IV over 24 hours day 1, ifosfamide 1500 mg/m^2 IV day 2–5 with mesna, and cisplatin 25 mg/m^2 IV day 2–5).[9,11] Except for omission of oxaliplatin, the first two cycles were identical to the GETUG-13 approach. In GETUG-13, bleomycin dose was reduced by at least 20% in 38% and 45% of patients in cycles 4 and 5, respectively.[7] With omission of oxaliplatin from these cycles and the questionable efficacy of the infusional bleomycin, we were concerned that cycles 4 and 5 provided little more than the equivalent of cisplatin-ifosfamide doublets. We intensified these cycles by using an additional cycle of T-BEP plus TIP, which has a known safety profile and proven effectiveness. This increased treatment intensity in cycles 4 and 5 to compensate for omission of oxaliplatin in cycles 2 and 3 (Table 1). Patients with clinical signs of bleomycin pulmonary toxicity or diffusing capacity for carbon monoxide/alveolar volume (DLCO/VA) less than 75% after two cycles of T-BEP received PEI (cisplatin 20 mg/m^2, etoposide 100 mg/m^2, and ifosfamide 1.2 gm/m^2 all IV days 1–5) instead of the third cycle of T-BEP.[12] Patients received prophylactic G-CSF with all cycles and mesna was given following ifosfamide.

Tumor markers and chest radiograph were obtained every three weeks. Lung function was assessed by spirometry and carbon monoxide diffusion at baseline and before cycle 4. Restaging whole-body computed tomography (CT) scan was done after completion of systemic therapy. Patients with residual masses more than 1 cm were assessed for surgical resection. Patients were followed after treatment once every

Table 1. Chemotherapy dosing schedule

	GETUG-13		T-BEP/TIP			T-BEP/PEI/TIP		
Drug	**Total dose (mg/m²)**	**Dose intensity (dose/week)**	**Total dose (mg/m²)**	**Dose intensity (dose/week)**	**(%)**	**Total dose (mg/m²)**	**Dose intensity (dose/week)**	**(%)**
Cisplatin	400	33.3	400	33.3	100	400	33.3	100
Etoposide	1000	83.3	1500	125	150	1500	125	150
Bleomycin*	430 U	35.8	270 U	22.5	63	180 U	15	42
Paclitaxel	350	29.2	775	64.6	221	600	50	171
Oxaliplatin	260	21.7	0	0	0	0	0	0
Ifosfamide	12000	1000	6000	500	50	12000	1000	100

*Total dose in units. Comparison of planned total dose and dose intensity of agents used during 12-week intensified chemotherapy period. PEI: cisplatin, etoposide, ifosfamide; T-BEP: three cycles of bleomycin, etoposide, cisplatin. TIP: paclitaxel, ifosfamide, cisplatin.

two months for two years, once every four months in the third year, once every six months in the fourth year, and once every year after the fourth year. Surveillance included clinical examination, tumor markers, and CT scan of the initially involved sites (every four months for two years, and then annually for the next three years). Outcome data were extracted retrospectively. Grade 3–5 toxicities were identified and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. PFS and OS was calculated from the date of initiation of chemotherapy.

Results

Between May 1, 2012 and April 30, 2016, 10 men with poor-prognosis GCC were identified: four had liver metastases, one had brain metastases, two had bone metastases, and one had a small bowel metastasis (Table 2). Eight had unfavorable tumor marker decline: seven had inadequate drop in AFP or HCG, and one had a rise in AFP, after their first BEP or VIP cycle. Six of these men were offered and received intensified chemotherapy; two were treated with standard BEP. Of the six patients treated with intensified chemotherapy, two received cycles 2–4 T-BEP plus cycle 5 TIP, and four received cycle 2–3 T-BEP, cycle 4 PEI, and cycle 5 TIP due to decline in DLCO/VA of greater than 25% after cycle 3. One patient was diagnosed with synchronous metastatic adenocarcinoma ex teratoma during intensified chemotherapy treatment. Two patients had a favorable tumor marker decline by virtue of normal markers pre-treatment and no rise in AFP or HCG after cycle 1 BEP, and received four cycles of BEP. Of the four patients treated with BEP, one had last-cycle BEP replaced with VIP for pulmonary toxicity.

The received dose intensity of the intensified chemotherapy was 100% of that planned for all drugs. Median time from start of first to start of last intensified chemotherapy cycle was 64.5 days (range 62–70) (expected time: 63 days). One patient with choriocarcinoma who had brain metastases and high-volume lung metastases received an initial cycle of EP, which was complicated by tumor lysis syndrome and multiorgan failure. No other serious pulmonary toxicity was observed (Table 3). After recovery, this patient received one cycle of VIP chemotherapy and then four cycles of intensified chemotherapy (total six cycles). Three patients experienced an episode of febrile neutropenia despite G-CSF prophylaxis. One patient experienced *C. difficile* colitis after cycles 2 and 4, one had culture-negative neutropenic proctitis, and one had neutropenic sepsis due to *E. coli* bacteremia. Two patients experienced deep venous thrombosis requiring anticoagulation.

All five patients with pure GCC treated with intensified chemotherapy achieved marker-negative partial response (PR). Four had post-chemotherapy retroperitoneal lymph node dissection (RPLND) along with right hepatic lobectomy and orchiectomy in one patient each. Postoperatively, one patient had ascites due to a pancreatic leak that has since

Table 2. Patient characteristics

	UTMD + intensified chemo (n=6)	UTMD + standard BEP (n=2)	Favorable TMD + standard BEP (n=2)
Age (years)	30 (20–51)	21, 32	18, 23
HCG >50 000 IU/L	1	1	0
AFP >10 000 ng/mL	4	0	0
LDH >10 x ULN	0	1	0
Extrapulmonary visceral metastases	4	0	2
Primary mediastinal NSGCT	0	0	0
ECOG performance status			
0	1	0	1
1	4	2	1
2–4	1	0	0

Data are median (range). UTMD + intensified chemo=patients with an unfavorable marker decline who received a dose-dense regimen. UTMD + Std BEP=patient(s) who received standard BEP prior to availability of GETUG-13 results. TMD inevaluable + Std BEP=patients who did not have assessable tumor marker levels but met criteria for poor prognosis disease by virtue of extrapulmonary visceral metastases. AFP: serum alfa-fetoprotein; ECOG: Eastern Cooperative Oncology Group; HCG: human chorionic gonadotropin; IGCCCG: International Germ Cell Cancer Collaborative Group; LDH: serum lactate dehydrogenase; NSGCT: non-seminomatous germ cell tumor; TMD: tumor markers decline; ULN: upper limit of normal; UTMD: unfavorable tumor marker decline.

Table 3. Adverse events

	UTMD + intensified chemo (n=6)			Standard chemotherapy (n=4)		
Toxicity grade	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 1–2**	**Grade 3**	**Grade 4**
Nausea or vomiting	4	0	0	2	1	0
Fatigue	4	0	0	2	1	0
Diarrhea	5	0	0	0	0	0
Liver	4	2	0	1	1	0
Sensory neuropathy	2	2	0	0	0	0
Dyspnea	4	0	1	2	1	0
Hemoglobin	1	4	1	2	2	0
Neutropenia	3	0	3	0	0	1
Thrombocytopenia	4	1	1	3	0	1
Febrile neutropenia	0	3	0	0	0	0
Infection	0	1	0	0	0	0
Deep vein thrombus	0	2	0	0	0	0

UTMD + intensified chemo=patients with an unfavorable marker decline who received a dose-dense regimen. Toxicity grade according to CTCAE 4.03. Infection=infectious event without neutropenic fever. UTMD: unfavorable tumor marker decline.

resolved. Pathology showed completely resected teratoma in two patients. Of four patients treated with standard BEP, one patient had complete response, two had marker-negative PR, and one had marker-positive PR. The latter patient had rapid relapse and died of treatment complications during the first cycle of salvage chemotherapy. One patient with marker-negative PR had hepatic resection demonstrating residual GCC and died of acute pulmonary embolism before starting salvage treatment.

There were no toxic deaths with intensified chemotherapy. One patient died of synchronously diagnosed metastatic adenocarcinoma ex teratoma after 27 months with peripheral sensory neuropathy requiring treatment with gabapentin. The five pure GCC patients treated with intensified chemotherapy are all alive at a median of 63.5 months (range 46.3-65.6). Four have no evidence of disease (NED) and one patient has residual teratoma being observed in consideration of the risks of repeat surgery. Four have returned to usual school or work, and the remaining patient has been unable to return to work due to grade 2 cognitive dysfunction. One patient who received a total of six cycles of chemotherapy experienced grade 3 peripheral sensory neuropathy now resolved to grade 2. Of the four patients who received standard BEP chemotherapy, two relapsed and died after 5.5 and 7.8 months, and two are NED at a median of 51.4 and 53.6 months.

Discussion

Although cure is expected for most men with metastatic GCC, poor-prognosis disease remains a challenge. In 1997, the IGCCCG reported just a 48% five-year OS in these patients.[1] Results have improved over the past 20 years due to incremental improvements in care delivery.[13] In the GETUG-13 trial, Fizazi et al[7] confirmed the prognostic validity of first-cycle tumor marker decline and a benefit of intensified chemotherapy in patients with an unfavorable decline. Three-year OS in patients treated with standard BEP chemotherapy was 84% in patients with favorable tumor marker decline and 65% in those with unfavorable decline. This confirms that results have improved but, as 80% of patients had an unfavorable tumor marker decline, there is still need further improvement in treatment. Fortunately, poor-prognosis GCC is uncommon, but this also makes it difficult to study. We identified only 10 patients with poor-prognosis GCC at our referral centre over a four-year period, and 80% had unfavorable tumor marker decline, identical to GETUG-13.

Despite the results of GETUG-13, intensified chemotherapy for patients with unfavorable tumor marker decline has not been widely adopted in North America. The reasons for this are not entirely clear, but concerns about the rationale, safety, and availability of drugs included in the intensified chemotherapy regimen used are likely. As oxaliplatin for curative GCC treatment remains unavailable in our jurisdiction, we modified the GETUG-13 intensified chemotherapy approach using standardized regimens familiar to medical oncologists treating GCC. T-BEP was developed by the European Organisation for the Research and Treatment of Cancer using a conventional drug development approach and was tested showing favorable results in intermediate-prognosis GCC in a phase 3 trial.[9,14] Compared to the GETUG-13 approach, our approach did not use oxaliplatin but provided an identical cisplatin dose, 50% higher etoposide dose, 121% higher paclitaxel dose, and 50% lower ifosfamide dose. In patients receiving cycle 4 PEI, cisplatin and ifosfamide doses were identical, etoposide was 50% higher, and paclitaxel 71% higher. These regimens were delivered at full dose and on schedule. Although open to critique, we propose that the increased etoposide and paclitaxel doses given with our approach more than adequately compensate

for the omission of two oxaliplatin doses and reduced total bleomycin dose compared to GETUG-13.

Although intensified chemotherapy was reasonably well-tolerated, the risks should not be trivialized. Serious complications occurred during treatment that included neutropenic sepsis despite G-CSF, *C. difficile* colitis, and deep venous thrombosis. More aggressive use of G-CSF prophylaxis may be warranted with our approach. The assessment and management of bleomycin pulmonary toxicity remains controversial. Shamash and colleagues[10] have suggested that routine pulmonary function testing is of little value, and that development of cough and findings on chest CT are better identifiers. We tended to be conservative, and four of six patients had PEI substituted for cycle 3 T-BEP due to decline in DLCO/VA of greater than 25%. Our intended bleomycin doses were no more than 34% and 56% less the doses actually received by patients in the GETUG-13 trial. Including cycle 1 BEP bleomycin, four patients received a total dose of 270 units of bleomycin, and one each received 240 units and 360 units. Two patients experienced grade 3 peripheral sensory neuropathy that resolved to grade 2 in one patient. One patient has not returned to usual work due to grade 2 cognitive disturbance and grade 1 dizziness. Increased paclitaxel exposure could contribute to both neuropathy and pulmonary toxicity.

Our report is limited by its small sample size; nevertheless, all five pure GCC patients treated with intensified chemotherapy remain alive at a median followup of nearly five years, which appears to be compatible with GETUG-13 (75% OS at five years), and no patients have required salvage HDCT. We demonstrate that intensified chemotherapy based on the GETUG-13 approach in patients with unfavorable tumor decline after one cycle of BEP chemotherapy is feasible in a Canadian setting. However, the use of intensified chemotherapy should be restricted to high-volume GCC centers, consistent with recent expert recommendations that poor-prognostic GCC patients be managed in this environment.[13]

Conclusions

Our experience to date suggests that use of intensified chemotherapy for men with poor-prognosis metastatic GCC and unfavorable tumor marker decline after one cycle of BEP is feasible and reasonably safe. Our outcomes appear to be similar to those reported in GETUG-13. Although GETUG-13 provided proof-of-principle for chemotherapy intensification, the optimal intensified chemotherapy regimen remains controversial. In our approach, we optimized doses of etoposide and paclitaxel using standard combination regimens to compensate for omission of oxaliplatin, which was unavailable, and reduced exposure to bleomycin. Peripheral sensory neuropathy was the most common long-term adverse effect noted, likely due to cumulative exposure to cisplatin and paclitaxel. Despite limited patient numbers, this report supports further investigation of dose-intensification in treating high-risk, poor-prognosis metastatic testicular cancer patients.

Competing interests: Dr. Ernst has received honoraria from Astellas, BMS, and Novartis. Dr. Fernandes has received honoraria from Bayer and Janssen. Dr. Winquist has received honoraria from Amgen, Bayer, Eisai, Merck, and Roche. The remaining authors report no competing personal or financial interests related to this work.

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Correspondence: Dr. Eric Winquist, Division of Medical Oncology, Department of Oncology, Western University and London Health Sciences Centre, London, ON, Canada; eric.winquist@lhsc.on.ca