The importance of the dose of etoposide in the initial treatment of metastatic germ cell tumors and advances in management of patients that relapse

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Objective: *The primary objective was to evaluate the effect of etoposide dose in a 3-day cisplatin/etoposide/bleomycin (PEB) regimen on progression free survival (PFS) and overall survival (OS). Secondary objectives were to determine the impact of a paclitaxel-based salvage regimen on OS and to compare the risk distribution of germ cell patients seen at a tertiary care center to that quoted in the International Germ Cell Consensus Classification (IGCCC).*
Methods: *A retrospective chart review of all 302 metastatic germ cell patients requiring cisplatin-based chemotherapy between January 1980 and December 2004 was conducted. Data collected on initial treatment included the dose of etoposide: 500 mg/m^2/cycle (E500) or 360 mg/m^2/cycle (E360) and whether the salvage treatment contained paclitaxel or not. PFS and OS were calculated. Patients were risk stratified as per IGCCC variables.*
Results: *The relapse rate and overall survival for E500 was 3% and 97% respectively compared to a relapse rate and OS rate of 29% and 80% respectively for E360. The addition of paclitaxel to salvage chemotherapy regimens for patients that relapsed results were 1/5 (20%) of patients dying compared to 26/39 (67%) for those who received a non-paclitaxel based salvage regimen.*
Ninety percent of seminoma patients were good risk and 10% were intermediate risk. Non-seminoma (NSGCT) patients were skewed to the good-risk category: 71% good risk, 10% intermediate risk and 18% poor risk as compared to 56%, 28% and 16% respectively as reported by the IGCCC. Five-year PFS and OS were comparable to those documented by the IGCCC with the exception of the intermediate risk NSGCT patients.
Conclusion: *This review demonstrated that PEB treatment containing higher dose etoposide was superior in terms of PFS and OS. Although the sample size was small, it appeared that paclitaxel containing salvage regimens resulted in superior outcomes compared to previously used salvage regimens. Our center had a similar risk distribution of patients as that quoted by the IGCCC.*

Key Words: germ cell tumor, testicular cancer, cisplatin, etoposide, paclitaxel, bleomycin, PEB, TIP, salvage, chemotherapy, testicular, IGCCC, vinblastine, VeIP, seminoma, non-seminoma, chemotherapy

Introduction

Germ cell tumors (GCT) are highly treatable, usually curable, cancers that occur primarily in young to middle-aged adult males. Seminomas and non-seminomas differ in their sensitivity to treatment modalities and stage at presentation, resulting in overall cure rates for seminomas exceeding 90% and for non-seminomas exceeding 80%.[1]

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Patients who have disseminated GCTs typically receive a first-line chemotherapy regimen of cisplatin, etoposide and bleomycin (PEB).[2] While PEB has been considered standard treatment for years, some centers have used an etoposide dose of 360 mg/m^2 per cycle ($PE_{360}B$) and others have used 500 mg/m^2 ($PE_{500}B$).[3] Most patients with advanced disease can be cured with either three or four cycles of PEB depending on their International Germ Cell Cancer Consensus Group (IGCCCG) risk classification.[4] However, 20%-30% of patients do not achieve a durable, complete response to PEB[5] and will require salvage therapy. For relapsing patients, either a standard dose chemotherapy protocol or a high dose chemotherapy approach with autologous

stem cell support can be utilized. One standard dose accepted salvage regimen consists of ifosfamide, cisplatin, and vinblastine (VeIP), which has a reported response rate of 25%-50%.[6,7] Recently, a regimen of paclitaxel, ifosfamide, and cisplatin (TIP) has been reported to yield up to an 80% response rate in a single institution phase II study[8] and has resulted in some centers adopting this as their initial salvage regimen. Another salvage therapy is high-dose carboplatin plus etoposide with or without ifosfamide, followed by stem cell rescue, which results in a complete response in 15%-25% of patients.[7,9]

The IGCCCG has developed a risk stratification tool to aid in identifying high, intermediate, and low risk patients with GCTs.[10] In addition to aiding clinicians in determining prognosis and assisting in directing chemotherapy regimen changes it has allowed for the comparison of outcomes from different centers and groups. Patients who are at risk for relapse are identified and may be eligible for more aggressive, intensive protocols while those with a better prognosis are spared the toxicity of intensive therapy i.e. three courses of PEB for low risk patients as opposed to the previous standard of four courses

In September of 2001, the oncologists at Cross Cancer Institute made two changes to the treatment protocols for metastatic GCTs: the dose of etoposide in PEB was escalated from 360 mg/m^2 to 500 mg/m^2, although still administered as a 3 day ambulatory care regimen, and the TIP regimen replaced VeIP as the primary salvage regimen for relapsing patients.

In this retrospective review, we report how these changes have impacted on the long-term disease control rates of patients treated in a single institution. Our institution's risk-stratified patient distribution and survival data was determined and compared to the values reported in the IGCCC study.

Patients and methods

Prior to data collection, the project was reviewed and approved by the Alberta Cancer Board Research Ethics Board. The Alberta Cancer Registry was used to identify all patients diagnosed with a metastatic germ cell tumor and treated with platinum based chemotherapy at the Cross Cancer Institute between January 1980 and December 2004. A total of 302 patients were eligible and were included in the study. Patients receiving adjuvant chemotherapy without metastatic disease were excluded from the study.

In addition to basic demographics, data on known risk factors as per the IGCCCG classification document were collected, including tumor site and histology, location of metastatic disease, and tumor marker levels including human chorionic gonadotropin [HCG], alphafetoprotein [AFP] and lactate dehydrogenase [LDH]. The dose of etoposide administered in the PEB regimen was recorded. The chemotherapy is given as a 3 day ambulatory care regimen with the cisplatin administered at a dose of 100 mg/m^2 over 3 days and the bleomycin 30 units/day administered as a 20 hour infusion for the 3 days.[11,12] Prior to 2001, a total of four cycles of PEB was given to each patient, whereas after 2001, some good risk patients may have received three cycles. If patients relapsed, the treatment given for the first and any subsequent relapse was also noted. PEB was not repeated if a patient relapsed on it initially. The TIP regimen was modified in that the dose of paclitaxel was reduced to 175 mg/m^2 in order for it to be administered in an ambulatory care setting over 4 days.[13,14] For all patients, overall and relapse free survival data was collected.

Statistical methods

Descriptive statistics of the seminoma and non-seminoma/mixed patient characteristics were produced. The univariate log-rank test was used to determine the significance of the prognostic factors in predicting overall and progression free survival. A "p" value of 0.05 was considered statistically significant. Kaplan-Meier survival curves were generated and the 5-year survival rates obtained for patients treated with lower versus higher dose etoposide as well as with TIP salvage chemotherapy versus other regimens. Overall survival (OS) was calculated from the date of diagnosis to death or date of last follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to date of relapse, death, or last follow-up. For univariate analyses, initial AFP (< 1000, ≥ 1000 and ≤ 10000, and > 10000 ng/mL), HCG (< 5000, ≥ 5000 and ≤ 50000 and > 50000 IU/L) and LDH (< 1.5 x upper limit of normal [N], ≥ 1.5x[N] and ≤ 10x[N], and > 10x N) were used on an ordinal scale.

Results

Patient characteristics

Of the 302 patients in the study, 235 (78%) patients had non-seminoma or mixed tumors. The risk stratification of non-seminoma patients was 169 good-risk (72%), 24 intermediate-risk (10%), and 42 poor risk patients (18%). The 5-year OS and PFS for good risk patients was 94% and 83%, respectively; for intermediate risk patients, 75% and 48%; and poor risk patients it was 50% and 34%. See Table 1.

TABLE 1. **Risk stratification values and estimated OS and PFS for the CCT and the IGCCC**

Prognosis	Non-seminoma/ mixed (n = 235)			Seminoma (n = 67)		
	Incidence (%)	OS (%)	PFS (%)	Incidence (%)	OS (%)	PFS (%)
Good	72 (56)	94 (92)	83 (89)	91 (90)	82 (86)	85 (82)
Intermediate	10 (28)	75 (80)	48 (75)	9 (10)	≤ 27 (72)	≤ 50 (67)
Poor	18 (16)	50 (48)	34 (41)	-	-	-

*IGCCC values are given in brackets

A total of 67 out of 302 (22%) patients had a seminoma. The risk stratification of seminoma patients was 61 (90%) good risk and 6 (10%) intermediate risk patients. The 5-year OS for the good risk patients was 82% and the 5-year PFS was 85%. The intermediate risk seminoma sample size was very small, with only six patients being stratified to this category. Data analysis was quite difficult in this subset of patients. We calculated the 5-year OS for the intermediate risk patients to be ≤ 27% and the 5-year PFS to be ≤ 50%, but these values are likely underestimated due to the small sample size. See Table 1. The survival curves generated for this subset of seminoma tumor patients was distorted and estimates of the outcome measures were made by data interpolation.

Overall survival of all 302 patients included in this study was 82% and the relapse rate was 26%. The median follow-up time for patients treated between January 1980 and September 2001 was 59 months and for patients treated between September 2001 and December 2004 was 38 months.

Dose escalation of etoposide

Of the 302 patients, 270 were treated between January 1980 and September 2001 and these patients received $PE_{360}B$ as their first line chemotherapy for metastatic disease. Twenty-nine (29) patients relapsed and OS for the entire cohort was 80%. After September 2001, 32 patients were treated with $PE_{500}B$. Only one patient relapsed (3%) and the OS was 97% for this group. See Figure 1.

Salvage treatment

Prior to September 2001, 75 patients relapsed. Thirty-seven patients had a nodal recurrence of their disease and were treated surgically with a resection or a retroperitoneal lymph node dissection. Thirty- eight patients relapsed and received salvage chemotherapy. VeIP was the combination used most often for patients

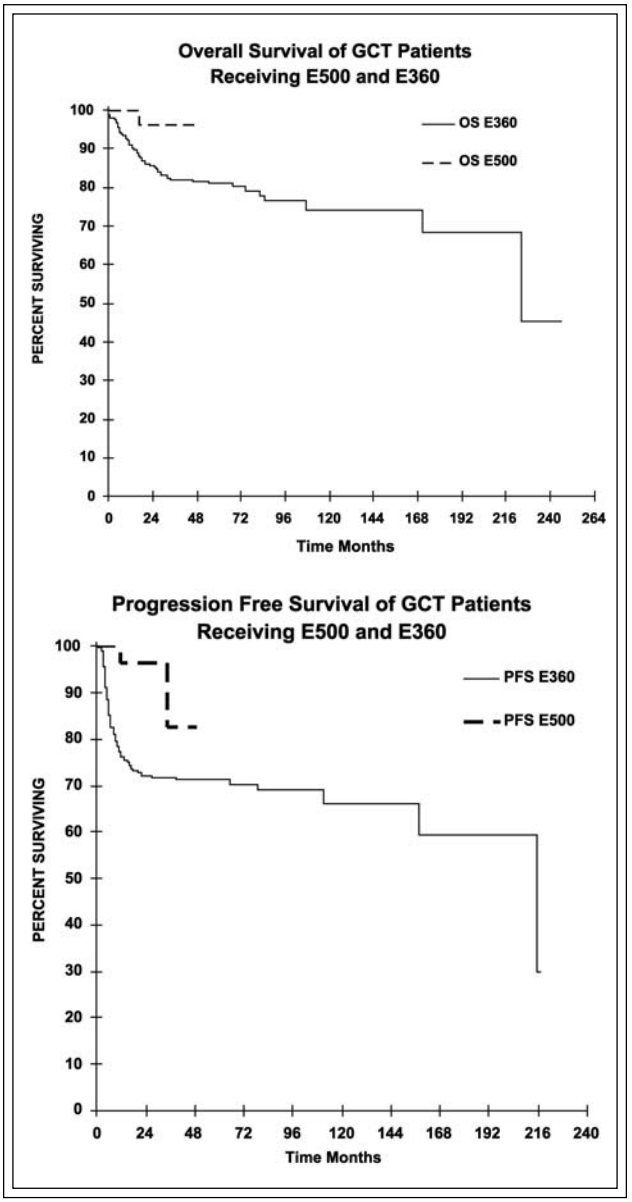

Figure 1. Survival times and progression free time in the patients receiving E360 and E500.

receiving standard dose treatment, with 20 of the 38 patients having it as their salvage treatment. Eight patients were given high dose therapy with stem cell rescue as their second or third line therapy. The remaining ten patients received non-standard salvage regimens that were not vinblastine based. Prior to September 2001, only 29% of patients receiving salvage treatments were cured of their disease, including three patients who were ultimately cured with high dose chemotherapy and stem cell transplantation. Of the patients receiving VeIP, 40% of patients ultimately survived, including two patients ultimately cured with high dose chemotherapy and stem cell transplantation. After September of 2001, five patients relapsed, all requiring salvage chemotherapy which consisted of the TIP regimen as described previously in the document. Only one patient has died of their disease representing an OS of 4/5 (80%).

Discussion

Germ cell tumors are highly curable malignancies, even if patients present with extensive metastatic disease. However, up to 30% of patients will recur after first line platinum based chemotherapy.[5] The challenge for clinicians is to determine who will ultimately do well and spare them excess toxicity of intensive treatment compared to those patients who are at higher risk of relapse and who may need more aggressive treatment strategies. The IGCCCG helps clinicians in this regard.

After the initial reports of the success of PEB chemotherapy, the regimen implemented at the Cross Cancer Institute contained etoposide at a dose of 360 mg/m^2/cycle which was commonly used, especially in Europe.[3] However, with the advent of shorter treatment programs for good risk patients (three cycles versus four of PEB) as well as further data demonstrating the importance of etoposide dose in patients where bleomycin could not be used due to toxicity, it appeared that an etoposide dose of 500 mg/m^2/cycle is required in order to achieve optimal cure rates.[4] At our center, 80 patients (26%) over the last 25 years have relapsed after receiving PEB; 29% of patients treated with $PE_{360}B$ but only 3% of patients receiving $PE_{500}B$. Thus, the concept of a higher dose for etoposide being important in achieving cure in GCT has been reconfirmed in this population. As the sample size of patients treated after 2001 is small, the possibility of statistical error is increased. Nonetheless, there is a 26% difference in relapse rates between the two groups of patients with the only major difference in the treatment protocol being the increased dose of etoposide, which probably accounts for this difference. Toner et al concluded in 2001 that $PE_{360}B$ is inferior to $PE_{500}B$ when comparing the two standard treatment regimens. Our data also supports this conclusion.

With the introduction of TIP as our standard salvage chemotherapy for relapsing patients, the OS rate for these patients appears to be superior to that in the earlier group of patients treated with other regimens such as VeIP. The cure rate for the earlier salvage regimens was 29% (cure rate for VeIP) which is quite inferior to that reported by Motzer[8] with TIP, granted it is not possible to directly compare these results from two different groups of patients, particularly as one was treated in a study setting and the other in a clinical practice setting.

Given the very small sample size in our patients treated with TIP, it is impossible to make definitive conclusions. However, it would appear that TIP is a highly active salvage regimen for appropriately selected patients with 4/5 patients treated at our center with TIP being alive and disease free. These results are similar to those of Motzer et al who conducted a trial of TIP salvage therapy in 30 patients and achieved complete response of 77% of patients and 85% were alive after a median follow up time of 33 months.[8]

In addition our regimen of paclitaxel doses at 175 mg/m^2 on day 1 followed by 3 days of ifosfamide and platinum administered in an ambulatory care setting may result in equivalent survival.[16] Empirically, these data suggests that for relapsing patients switching to a paclitaxel-based salvage regimen would be the preferred treatment strategy for those who meet the eligibility criteria for standard dose therapy, namely having platinum sensitive disease. We believe that for platinum sensitive patients, TIP should be the standard second line salvage treatment for patients being salvaged with standard dose chemotherapy and we would reserve high dose chemotherapy for patients relapsing after TIP.

The data compiled by the IGCCC is from an international database of patient information from cancer treatment facilities around the world. The Cross Cancer Institute is a tertiary center serving a population of approximately 1.6 million people and has a distribution of patients that is comparable to the international standard. The distribution of seminoma patients was similar to the IGCCC, see Table 1, whereas the non-seminoma (NS) patients were skewed in that there was a higher proportion of good risk patients and a lower proportion of

intermediate risk patients. Five-year PFS and OS were comparable to those documented by the IGCCC with the exception of the intermediate risk NS patients: 5-year PFS was 48% compared to 75% expected but 5-year OS was similar in these patients (75% versus 80%). This difference may be due to the relatively small sample size in our series. The OS for all patients in the study was 82%, which is the similar to that reported in the literature.[1] Our survival data for stem cell rescue patients (38%) is also comparable to studies done in other centers reporting between 25% and 40% survival.[1]

As previously mentioned, a major limitation of this study was the small sample size in some cohorts of patients, particularly the intermediate-risk seminoma patients and the relapse patients receiving TIP salvage chemotherapy. We also recognize that by the nature of the study, the two cohorts, pre and post 2001, are not balanced. Nonetheless, it would appear that cure rates for metastatic testicular cancer are superior in the post-2001 era correlating with the changes made to our treatment approach.

In summary, in order to achieve optimal outcomes for patients with metastatic germ cell cancers, the dose of etoposide is critical. Specifically, the dose of etoposide in first line PEB chemotherapy should be administered at 500 mg/m^2 each cycle. For patients that relapse with platinum sensitive disease, TIP can be considered a standard salvage regimen with high dose chemotherapy and stem cell transplantation reserved for third line treatment. The IGCCC criteria for stratifying patients is useful in the clinical setting as our center, a tertiary academic cancer treatment center, does have a similar risk distribution of patients and treatment outcomes and survival are comparable to the published world literature. □

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