RESEARCH COMMUNICATION

Bleomycin, Etoposide and Cisplatinum (BEP) Chemotherapy for Metastatic Germ Cell Tumours: Treatment Outcomes at UKM Medical Centre, Malaysia

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Abstract

Introduction: Although bleomycin/etoposide/cisplatinum (BEP) chemotherapy is established as the standard treatment for germ cell tumours, it requires significant experience in administration and toxicity management to maintain optimal dose intensity. A retrospective review of 30 patients was conducted at UKMMC to study treatment outcomes. Methods & Materials: Patients with GCTs and treated with at least two cycles of BEP chemotherapy between January 2003 and Oct 2009 were eligible for this study. Patients received 4-6 cycles of bleomycin 30,000IU IV D1, D8 & D15 and either etoposide 100mg/m^2 IV D1- D5 and cisplatin 20mg/m^2 IV D1-D5 (5 day BEP regimen) or etoposide 165mg/m^2 D1- D3 and cisplatin 50mg/m^2 D1-3 (3 day BEP regimen) every three weeks per cycle. All patients received prophylactic granulocyte colony-stimulating factor (GCSF) from days 6 to 10 of each cycle. The overall response rates, 2 year progression-free survival and overall survival of the whole cohort were assessed. Results: Thirty patients fulfilled the inclusion criteria. Non-seminomatous GCTs comprised 93.3% of cases and gonadal and mediastinal primary sites were the most common. Sixty percent were classified as IGCCCG poor risk disease. Median follow-up was 26.6 months. The overall response rate (CR+PR) was 70%. The two year PFS and OS were 70% and 66%. There was a significant difference in terms of the overall response rate (85% vs 40%, p = 0.03) and in PFS (94.7% vs 50%, p = 0.003) between gonadal and extragonadal primary sites. Conclusion: It is possible to achieve outcomes similar to those in international clinical trials with close monitoring and good supportive care of patients undergoing BEP chemotherapy. There is a strong argument for patients with IGCCCG poor prognosis disease to be treated in specialist tertiary centres to optimize treatment outcomes.

Keywords: Germ cell tumour - BEP chemotherapy - prognosis - Malaysia

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Introduction

Prior to the introduction of cisplatinum based chemotherapy, the outcome for metastatic germ cell tumours (GCT) was dismal with survival rates of less than 5%. Subsequent research has established bleomycin, etoposide and cisplatinum (BEP) chemotherapy as the standard of care for this disease with dramatic improvements in survival. The formation and wide spread acceptance of the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic factor based staging system for metastatic germ cell tumours has allowed the definition of good, intermediate and poor prognostic groups with cure rates of 90%, 80% and 45%, respectively for non-seminomatous GCTs (IGCCCG, 1997).

According to the 2006 Malaysian National Cancer Registry Report (NCR), there were 330 new cases of testicular cancer and 1017 new cases of ovarian cancer diagnosed between 2003 and 2005 in Peninsular Malaysia (Gerard et al., 2008). Approximately 10% of the ovarian cancers were germ cell tumours. Epidemiological data indicate that 90% of GCTs are testicular in origin.

As the BEP chemotherapy schedule is complex and maintaining the optimal chemotherapeutic dose intensity is important in achieving the high cure rates seen in this disease, considerable experience in the management of patients with GCT is necessary. Consequently, a retrospective study was conducted on patients diagnosed with germ cell tumours who were treated at University Kebangsaan Malaysia Medical Centre (UKMMC), with a view to assessing treatment outcomes in the Malaysian setting.

Materials and Methods

Patients diagnosed with germ cell tumours and treated with at least two cycles of BEP chemotherapy between January 2003 and Oct 2009 in Universiti Kebangsaan Malaysia Medical Centre were eligible for this study. Patients without histopathological confirmation were included if they had typical clinical features and

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markedly raised AFP, β-HCG and LDH. Patients who presented to UKMMC with recurrent or relapsed GCTs and were treated with non-BEP regimens were excluded from this study. Case notes were traced via the Medical Records office and relevant clinical data were obtained retrospectively. Patients who were lost to follow-up were contacted to determine their current status. Those who were not contactable were censored as status unknown. Survival data was obtained from the Malaysian National Registry of Births and Deaths.

Whenever possible, the diagnosis of GCTs would be confirmed histopathologically. Computed tomography of the chest, abdomen and pelvis would be done for staging purposes prior to chemotherapy. Routine blood investigations (full blood count, renal profile, liver function tests) would be done as part of the initial assessment. Sperm banking would be offered to suitable patients. Audiometry and lung function tests would only be done if there was concern regarding the function of the relevant organs.

The current standard chemotherapy for GCTs in UKMMC is bleomycin, etoposide and cisplatin (BEP). Two BEP regimens are commonly used in the department - bleomycin 30,000IU IV D1, D8 & D15, (maximum 300,000IU), etoposide 100mg/m^2 IV D1- D5 and cisplatin 20mg/m^2 IV D1-D5 (5 day BEP regimen) or bleomycin 30,000IU D1, D8 & D15 (maximum 300,000IU), etoposide 165mg/m^2 D1-D3 and cisplatin 50mg/m^2 D1-3 (3 day BEP regimen) every three weeks per cycle for 4-6 cycles. Routine blood investigations would be done prior to each cycle of chemotherapy. Patients would be reviewed weekly and chemotherapy adverse events treated accordingly. Prophylactic granulocyte colony-stimulating factor (GCSF) would be administered to all patients from day 6 to 10 of each cycle to reduce the risk of febrile neutropenia and to maintain dose intensity.

Upon completion of treatment, the patients would be reviewed every 1-3 months for the first year and then at three monthly intervals thereafter. At each visit, a physical examination would be done as well as blood tests for AFP, β-HCG and LDH. If there was a significant increase in any of the tumour markers, a CT scan would be performed to exclude recurrence.

Patients who had significant residual disease after chemotherapy would be referred to the surgical team for assessment of resectability. If the disease was not resectable, second line chemotherapy with VIP (vinblastine, ifosfamide and cisplatin) or TIP (paclitaxel, ifosfamide and cisplatin) would be offered. Occasionally, radiotherapy was given for limited local disease or palliation.

Statistical analysis was performed using SPSS version 16.0 software. Response rates were analysed using univariate analysis and survival data analysed by the Kaplan Meier method. Univariate and multivariate analyses were carried out to examine the relationship between patient demographics, ECOG status, primary site, IGCCCG status, chemotherapy dose density, number of chemotherapy cycles and response rate. Overall survival and progression free survival were analysed using the Kaplan-Meier method.

Results

A total of 44 patients with GCT were identified. Thirty patients with newly diagnosed GCT fulfilled the criteria for inclusion into the study. The other fourteen patients were excluded because of missing medical records (2), cancers of unknown primary (2), recurrent GCT (5), did not receive BEP as they had stage I testicular seminoma (2), non germ cell cancer of the testis (1) and did not complete at least 2 cycles of chemotherapy (2).

Patients' demographics are summarized in Table 1. The median age at diagnosis was 25 years old (15-47 years). The majority (66.7%) were less than 30 years of age. Most patients were male and of Malay ethnicity. Non-seminomatous germ cell tumours comprised 93.3% of patients and gonadal and mediastinal primary sites were the most common. Eighteen of thirty patients (60%) were classified as IGCCCG poor risk disease. Median follow-up was 26.6 months.

Chemotherapy details are summarized in Table 2. Most patients (86.7%) received at least 3 cycles of chemotherapy. The majority of patients received the 5 day BEP regimen. The median number of chemotherapy cycles was four for patients with IGCCCG good prognosis disease and six for those with poor prognosis disease. The overall response rate (complete and partial response) was 70%. Only two patients progressed during chemotherapy. There was a significant difference in terms of the overall response rate between gonadal and extragonadal primary sites (85% vs 40%, p = 0.03). All other characteristics

Table 1. Patient and Disease Characteristics and Summary of Chemotherapy

		N	(%)
Patient and Disease Characteristics			
Gender	Male	24	(80%)
	Female	6	(20%)
Ethnicity	Malay	23	(76.7%)
	Chinese	4	(13.3%)
	Indian	2	(6.7%)
	Other	1	(3.3%)
ECOG PS	0-1	22	(73.3%)
	2-3	8	(26.7%)
Histology	Seminoma	2	(6.7%)
	Non-seminoma	28	(93.3%)
Primary site	Gonadal	20	(66.7%)
	Intra-abdominal	2	(6.7%)
	Mediastinum	7	(23.3%)
	Brain	1	(3.3%)
IGCCCG Prognostic Group	Good	9	(30%)
	Intermediate	2	(6.7%)
	Poor	18	(60%)
	Undefined	1	(3.3%)
Summary of Chemotherapy			
BEP regimen	3 day regimen	2	(6.7%)
	5 day regimen	28	(93.3%)
Cycles administered	<4	6	(20%)
	5-6	22	(73.4%)
	>6	2	(6.6%)
Response	Complete response	9	(30%)
	Partial response	12	(40%)
	Stable disease	7	(23.3%)
	Progressive disease	2	(6.7%)

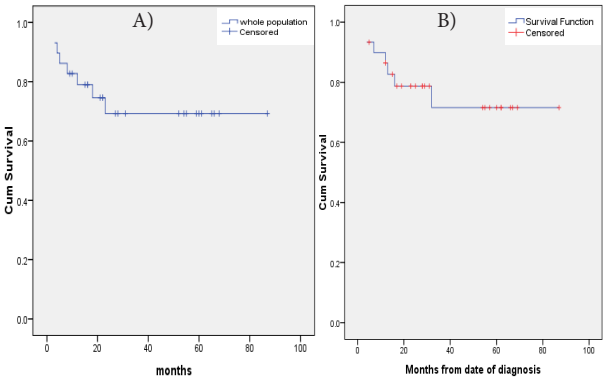

Figure 1. A) Progression Free Survival, B) Overall Survival.

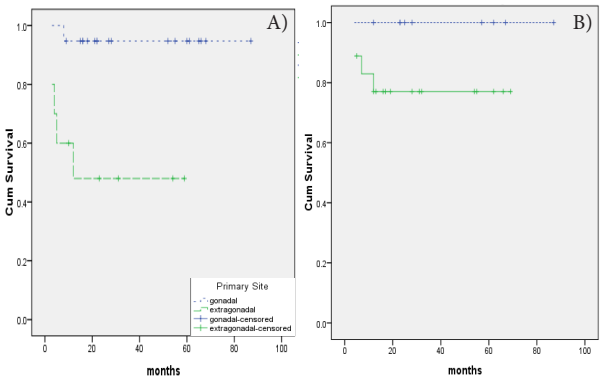

Figure 2. A) PFS According to Primary Site, B) OS According to IGCCCG Prognostic Group.

including IGCCCG prognostic group and chemotherapy dose density were not significant ($p > 0.05$). The overall response rate between the good and poor prognostic groups were 77.8% and 61.1% respectively ($p = 0.667$). Despite the routine use of prophylactic GCSF, a dose intensity of more than 90% for the BEP regimen was only achieved in approximately half of the patients and, furthermore, 20% of the patients developed febrile neutropenia while on treatment.

Figures 1A and 1B illustrate the progression free (PFS) and overall survival (OS) for the whole cohort. The two year PFS was 70%. There was a statistically significant difference in PFS between gonadal and extragonadal primary sites (94.7% vs 50%, $p = 0.003$) (Figure 2A). There was a trend towards better survival for IGCCCG good risk compared to poor risk disease (100% vs 64.7%, $p=0.052$). Surprisingly, there was also a borderline statistically significant difference in 2 year PFS between Malay and non-Malay patients (87.0% vs 50.0%, $p=0.05$).

The two year OS for the whole cohort was 66.6%. There was a significant difference between Malay and non - Malay patients (95.7% vs 57.1%, $p=0.006$). In addition, patients with a gonadal primary site had a better 2 year OS compared to those with extragonadal primaries (100% vs 60%, $p = 0.002$). As observed with PFS, there was no significant difference in OS between the good and poor prognostic groups (100% vs 77.8%, $p=0.131$) (Figure 2B).

Further analysis was performed using Cox regression analysis. The co-variates that were analysed included race, primary tumour site, IGCCCG prognostic groups and ECOG status. Extragonadal GCTs were found to have a 14.5 x higher risk of death compared to gonadal GCTs though the 95% confidence interval was very wide due to the small sample size ($p=0.033$, 95% CI 1.3 -168.3). The other factors studied were not found to be significant.

Discussion

This cohort of patients with germ cell tumour treated with BEP chemotherapy had a two year PFS of 70% and OS of 66.6%. In addition, patients with IGCCCG poor prognosis disease had a 2 year PFS and OS of 64.7% and 77.8%. This compares favourably with the results from international clinical trials where a 2 year OS of 70-80% were observed (Kaye et al., 1998; Culine et al., 2008).

Several interesting observations arose from this study. Firstly, 60% of patients in this cohort had poor prognosis disease. According to the IGCCCG classification system, patients with poor prognostic disease comprise only 16% of all NSGCTs and have a 5 year OS of 48%. This significantly higher incidence of IGCCCG poor prognosis disease among Malaysian patients may be due to the small sample size. However, this observation warrants further investigation with the collaboration of other centres that treat GCTs in Malaysia. Secondly, Malay patients appear to have a significantly better survival outcome as compared to non-Malay patients. This may be explained by poor prognosis disease being relatively commoner in non-Malay patients as compared to Malays (86% vs 60%). Thirdly, patients with extragonadal primaries had poorer PFS and OS compared to those with gonadal primaries. As mediastinal primaries formed the majority of extragonadal sites (7 of 10 patients) in addition to conferring an adverse prognosis, this may explain the poorer outcome seen in patients with extragonadal primaries.

Good prognosis NSGCT have a 5 year OS of 92% with BEP chemotherapy. As a result, many trials have been conducted to investigate methods to reduce the toxicity of treatment while maintaining cure rates in this good prognostic group. These trials have confirmed the detrimental effect of omitting bleomycin from BEP with a reduction in survival rates despite the risk of pneumonitis with its inclusion (Levi et al., 1993; Loehrer et al., 1995; De Wit et al., 1997). In addition, cisplatin instead of carboplatin is the preferred platinum agent to be used (Bokemeyer et al., 1996; Horwich et al., 1997). However, reducing treatment cycles from 4 to 3 appears possible without jeopardizing survival. The EORTC/MRC trial with 812 patients comparing 3 to 4 cycles of BEP chemotherapy found equivalent efficacy and toxicity between the two arms (de Wit et al., 2001). An earlier US trial compared 3 and 4 cycles of BEP in 184 patients and found similar survival but less toxicity with the shorter treatment arm (Einhorn et al., 1989).

On the other hand, randomized clinical trials investigating new treatment regimens have failed to improve the outcome for the IGCCCG poor prognostic group. In general, the two main approaches explored have been either modifying BEP by substitution or addition of other active drugs or high dose chemotherapy and autotransplantation. The French GETUG trial compared

vinblastine, etoposide, cisplatin and bleomycin with a slightly modified regimen followed by high dose cyclophospamide and etoposide, double-dose cisplatin and bone marrow support in 115 patients with mainly poor risk disease. They found a poorer outcome with the high dose approach (Droz et al., 2007). In addition, a US trial that compared a standard four cycles of BEP to two cycles of BEP followed by two cycles of high dose cyclophosphamide, etoposide and carboplatin in intermediate and poor risk disease did not show any survival improvement with the latter regimen (Bajorin et al., 2006). These trials have been criticized as using a suboptimal high dose chemotherapy regimen as the majority of patients died due to early disease progression. The alternative approach of modifying BEP has been extensively investigated in phase 3 trials but none have shown significantly better outcomes compared to the standard BEP regimen (De Wit et al., 1995; Nichols et al., 1998). The current approach of four cycles of BEP followed by 2 cycles of EP as practiced in UKMMC is based on the EORTC/MRC trial comparing BOP/VIP-B to BEP/EP where response rates and survival were similar (2 year OS 70-80%) but toxicity was less with the latter regimen (Kaye et al., 1998).

Treatment at larger tertiary referral centres have been demonstrated to confer better outcomes compared to smaller centres, probably due to improved multidisciplinary care (Aass et al., 1993; Harding et al., 1993). In a MRC/EORTC trial in intermediate and poor prognosis patients, centres which entered 5 or more patients achieved a 77% 2 year survival compared to centres entering fewer than 5 patients where survival was 62% (Collette et al., 1999). This difference most likely reflects experience in delivering the chemotherapy protocol, improved toxicity management and more aggressive use of surgery. A major implication of this observation is that poor risk patients should be treated in specialist tertiary centres where the necessary oncological and surgical expertise can be concentrated and outcomes further improved.

In conclusion, this study noted a higher than expected incidence of IGCCCG poor prognosis GCTs among Malaysians treated in UKMMC. The PFS and OS of the cohort of patients treated in UKMMC are similar to those in clinical trials. There is a strong argument for patients with IGCCCG poor prognosis disease to be treated in specialist tertiary centres to maximize treatment outcomes.

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