Etoposide and Cisplatin Chemotherapy for Metastatic Good-Risk Germ Cell Tumors

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ABSTRACT

Purpose
To assess response, overall survival, and relapse-free survival of patients with good-risk metastatic germ cell tumor (GCT) by International Germ Cell Consensus Classification Group (IGCCCG) criteria treated with four cycles of etoposide and cisplatin (EP).

Patients and Methods
Two hundred eighty-nine patients with IGCCCG good-risk GCT were treated with four cycles of EP. EP consisted of four cycles of etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 to 5 every 21 days.

Results
Two hundred eighty-two of 289 patients (98%) achieved a complete response; 269 (93%) responded to chemotherapy alone and 13 (5%) responded to chemotherapy plus surgical resection of viable disease (GCT other than mature teratoma). Seventeen (6%) experienced relapse, and nine (3%) died as a result of disease at a median follow-up of 7.7 years (range, 0.4 to 21.1 years). Sixty-two of 204 patients (30%) with nonseminoma had findings of teratoma or viable GCT at postchemotherapy surgery.

Conclusion
Four cycles of EP is a highly effective therapy for patients with good-risk GCT, with a high cure rate, low relapse rate, and little evidence of late relapse. Postchemotherapy surgery resection of residual disease remains an important aspect of treatment for these patients. Four cycles of EP is acceptable as a standard regimen for the treatment of good-risk metastatic GCT, and serves as an alternative to three cycles of bleomycin and etoposide before cisplatin.

INTRODUCTION

Nearly 80% of patients with metastatic germ cell tumors (GCTs) achieve a complete response (CR) to etoposide and cisplatin (EP) with/without bleomycin combination chemotherapy followed by adjunctive surgery. Efforts to improve efficacy and minimize treatment-related toxicity focus on the development of prognostic models with treatment tailored according to risk. Prognostic models developed in the 1980s were based on primary site, extent of disease, and serum tumor markers. These were used in clinical trials that have defined standard treatment for advanced GCT. The existence of multiple models was recognized as a disadvantage, and led to a collaboration by the International Germ Cell Cancer Collaborative Group (IGCCCG) to develop a classification algorithm. This model is now being used both for risk-directed clinical trials and in standard management to select appropriate chemotherapy treatment.

For patients with good-risk GCT, maintaining the high cure rate and minimizing treatment-related toxicity have been the goals of therapy. Two randomized trials were conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) in patients with good-risk...
EP for Metastatic Good-Risk GCTs

Three hundred eighty-nine patients treated with EP at MSKCC between November 1982 and December 2002 were the subject of this retrospective review. Two hundred eighty-nine had metastatic GCT and met the criteria for good-risk by IGCCCG criteria. All of the patients were treated on one of three prospective randomized trials or had consented to be part of an Institutional Review Board–approved comprehensive database.\(^2,3\)

MSKCC risk criteria\(^4\) had been used to assign good-risk status prospectively until August 1994. Thereafter, the IGCCCG criteria were used.\(^1\) For this review, the clinical features of all patients were reviewed and risk status retrospectively classified according to the IGCCCG criteria. Henceforth, good-risk refers to classification by IGCCCG criteria, and is reported by that method for this retrospective analysis.

The treatment plan of four cycles of EP has been described previously.\(^2,3\) To summarize, EP was administered at 3-week intervals for a total of four cycles. Cisplatin was administered at 20 mg/m\(^2\) on days 1 to 5 and etoposide was administered at a dose of 100 mg/m\(^2\) on days 1 to 5 of each cycle. No dose attenuation was permitted for neutropenia, nor did patients receive hematopoietic growth factors as part of routine supportive care. Serum tumor markers including human chorionic gonadotropin, alpha-fetoprotein, and lactate dehydrogenase, were obtained before, during, and at the completion of each cycle of chemotherapy. All initial sites of disease were evaluated radiographically (computed tomography of chest, abdomen, and pelvis) before and at the end of the four cycles of chemotherapy. Surgical excision of masses was performed routinely for patients with residual disease on radiographs or physical examination, and normal values of alpha-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase. After surgery, no additional chemotherapy was given if either mature teratoma or necrotic debris was present in the resected specimen. Two additional cycles of EP chemotherapy were administered to patients with complete resection of all residual disease if any site contained viable GCT.

Response was classified as either CR or incomplete response.\(^6\) A CR to chemotherapy was defined as the disappearance of all clinical, radiographic, and biochemical evidence of disease, or when all resected masses contained necrotic debris, fibrosis, or mature teratoma. A CR to chemotherapy plus surgery was indicated when serum tumor marker concentrations were normal and all residual disease was resected, but viable GCT was found at one or more site(s). Any response less than a CR was considered to be an incomplete response. Overall survival was defined as the time from chemotherapy initiation to death or last follow-up. Relapse-free survival is defined for complete responders only and is the time from chemotherapy initiation to relapse or last follow-up. Both curves were generated using the Kaplan-Meier method.\(^7,8\) Late relapse was defined as relapsed disease more than 2 years from the date of completion of therapy, in the absence of a second primary tumor.

**RESULTS**

**Patient Characteristics**

Eighty patients (28%) had pure seminoma and 209 patients (72%) had nonseminoma. (Table 1). The primary site was testis in 277 patients (96%), retroperitoneum in seven patients (2%), and mediastinum in five patients (2%; Table 1).

**Response to Treatment**

A CR was achieved in 282 of 289 assessable patients (98%; Table 2). This included 269 patients (93%) who achieved a CR to chemotherapy alone and an additional 13 patients (5%) who achieved a CR to chemotherapy plus...
surgical resection of viable disease (GCT other than mature teratoma). Seven patients (2%) failed to achieve a CR (best response of an incomplete response).

**Relapse-Free and Overall Survival**

Two hundred seventy-three of the 289 patients (94%) were alive with no evidence of disease at time of last follow-up. The median survival has not been reached, and the 5-year survival is 96% (95% CI, 94% to 98%; Fig 1), with a median follow-up for the survivors of 7.7 years (range, 0.37 to 21.1 years).

Nine patients (3%) died as a result of disease (Table 2). Three (1%) patients died as a result of unknown causes. These patients were without evidence of disease at last follow-up at 2.0, 2.1, and 18.8 years after completion of treatment, and were lost to follow-up thereafter. Four patients died as a result of other causes, including one patient with M4 acute myelogenous leukemia with inversion of chromosome 16.

The 5-year relapse-free survival for the 282 complete responders is 94% (95% CI, 91% to 97%; Fig 2), with a total of 17 relapses (6%). Fourteen of the relapses occurred within 2 years after the end of chemotherapy, with three late relapses at 2.7, 2.8, and 8 years from end of chemotherapy.

**Postchemotherapy Surgery for Nonseminoma**

One hundred thirty-four patients of 204 patients with nonseminoma who achieved a CR underwent postchemotherapy surgical resection of residual disease and 70 did not. Fifty-one of the 204 (25%) patients had pathologic findings of teratoma resected from residua, 11 (5%) had viable GCT (other than mature teratoma) resected, and 72 patients (35%) had only necrosis or fibrotic debris resected. Therefore, 62 of 204 patients (30%) had findings of teratoma or viable GCT at postchemotherapy resection.

**DISCUSSION**

This retrospective analysis of the MSKCC experience with four cycles of EP chemotherapy for good-risk GCT by IGCCCG criteria showed that there was a CR rate of 98%, with a relapse rate of 6% at a median follow-up of 7.7 years. The toxicity associated with this therapy has been described previously.2,3 In general, when compared with other cisplatin-combination programs used in the treatment of advanced GCT, four cycles of EP is well tolerated.2,3 Our studies have shown that four cycles of EP is associated with a high CR proportion, relative tolerability, and response durability.
During the last two decades, the goal of treatment for GCT patients predicted to have good prognosis by risk-classification systems has been to achieve patient cure with reduced treatment-related toxicity. Strategies to decrease treatment toxicity for good-risk GCT patients have included eliminating bleomycin, substituting carboplatin in place of cisplatin, and decreasing the number of chemotherapy cycles. Results of phase III randomized trials conducted at MSKCC showed that carboplatin was inferior to cisplatin in combination with etoposide, and that bleomycin could be eliminated from therapy when four cycles of EP chemotherapy are administered.\(^3\)

Two randomized trials have compared the efficacy of four cycles of EP to bleomycin, etoposide, and cisplatin (BEP) in good-risk GCT therapy. One randomized trial performed by the European Organization for the Research and Treatment of Cancer (EORTC) compared four cycles of BEP versus four cycles of EP chemotherapy.\(^2\) In this trial, the CR rate was lower in the EP arm, but there were no differences in relapses, time to progression, or survival after long-term follow-up. The dose of the etoposide in the EORTC trial was 360 mg/m\(^2\) per cycle. In addition, doses of etoposide were further reduced for thrombocytopenia. In the EP regimen used in randomized trials in the United States, 500 mg/m\(^2\) of etoposide is used and it is administered without dose reductions. A randomized trial comparing two regimens, one with 360 mg/m\(^2\) of etoposide and the other with 500 mg/m\(^2\) etoposide, indicated that the higher dose of etoposide may have contributed to the better outcome in that arm.\(^10\) Hence, the lower CR rate in the EORTC trial is likely due to an inadequate etoposide dose. The BEP arm in the EORTC trial was also more toxic, with resulting pulmonary toxicity and Raynaud’s phenomenon.\(^9\)

A second randomized trial compared three cycles of BEP chemotherapy versus four cycles of EP chemotherapy.\(^11\) Analysis of the primary end point of the trial (ie, the proportion of patients with a favorable response) was equivalent for BEP and EP. After a 4-year follow-up, the authors reported that the event-free survival was superior in the BEP arm. However, this trial was flawed in several aspects. In the analysis of event-free survival, patients who had a CR to chemotherapy plus surgery (ie, resection of viable GCT in residual masses postchemotherapy) and patients who experienced relapse with mature teratoma histology, were classified as having events.\(^11\) In prior reports of GCT trials, these occurrences have not been classified as treatment failures. This study was underpowered to detect superiority of one regimen or establish noninferiority, and tested multiple end points, thereby increasing the risk of false-positive conclusions. These specific points were raised regarding the trial design and its interpretation in a review of the presentation of this study at the Annual Meeting of the American Society of Clinical Oncology, which concluded that four cycles of EP remains an alternative treatment option to three cycles of BEP in good-risk GCT.\(^12\)

Complete resection of residual disease provides significant benefit because persistent teratomatous elements in the retroperitoneum may grow and could potentially obstruct or invade into adjacent structures and become unresectable. In addition, there is the risk of malignant transformation to non–germ cell somatic elements such as sarcoma or carcinoma, which may be present within these masses. Lastly, there may be a higher risk of late relapse if residual disease is not fully resected.\(^13\) In this study, the importance of postchemotherapy surgery is demonstrated by the findings of teratoma in 25% of patients, and of viable GCT in 5%, consistent with previous reports.\(^14,15\) Therefore, postchemotherapy surgical resection of residual disease remains an important aspect of treatment for these patients.

In summary, four cycles of EP with etoposide 100 mg/m\(^2\) daily for 5 days and cisplatin 20 mg/m\(^2\) daily for 5 days administered every 3 weeks, with surgical resection of residual disease, constitutes effective therapy for patients with good-risk GCT. We demonstrate that the response and cure rate is high (> 95%), and the relapse rate is low (6%). Four cycles of EP is acceptable as a standard regimen for the treatment of good-risk metastatic GCT, and serves as an alternative to three cycles of BEP. Four cycles of EP may be preferred in patients at high risk for pulmonary toxicity.

**Authors’ Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.

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**REFERENCES**


