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Tumor Marker Rise during Second Course of High-Dose Chemotherapy in Cancer: Outcome Analysis

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Abstract

Purpose: To retrospectively analyze the frequency and outcome of hCG and AFP rise at start of or within 1 week after initiation of second course of high-dose carboplatin and etoposide chemotherapy (HDCE) in patients with relapsed or refractory germ cell cancer.

Patients and methods: A single-institution review of 391 patients treated with HDCE and peripheral blood stem cell rescue from Feb 1996 to December 2010 was performed. Each patient received 2 consecutive courses of 700 mg of carboplatin per square meter of body-surface-area (BSA) and 750 mg of etoposide per square meter of BSA, each for 3 consecutive days, and each followed by autologous stem cell infusion. The second HDCE was administered 3-4 weeks after the first course. Weekly tumor markers were obtained.

Results: 25 of 391 (6.4%) patients were noted to have rising hCG, AFP or both at initiation or within 1 week of second course of HDCE. Fourteen patients had hCG rise (median 48.7 mIU/mL; range 3.2 – 8.863) and 11 AFP rise (median 18.3 ng/mL; range 4.2 - 1,018.8). Twenty-four of 25 patients had a subsequent decline in tumor marker with second course HDCE. Seven of 25 (28%) patients are continuously disease-free at median followup of 69 months (range 28-124 months).

Conclusion: Tumor marker rise during second course of HDCE is uncommon. Although it represents an adverse prognostic variable, cure is still possible with institution of second course of HDCE.

Keywords: Tumor marker; Germ cell cancer; HDCE

Introduction

Metastatic germ cell tumors are highly chemo-sensitive with cure rates as high as 90-95% for good-risk disease, 75% with intermediate-risk disease and 40-50% with poor-risk disease [1].

Refractory or relapsed disease continues to be an issue in 20-30% of the patients. Standard dosage salvage chemotherapy includes cisplatin plus ifosfamide with either vinblastine [2] or paclitaxel [3] for 4 courses, or high-dose chemotherapy with carboplatin and etoposide (HDCE) followed by autologous peripheral-blood stem cell rescue [4-6]. Einhorn et al. published data on 184 patients treated with HDCE with 63% of patients continuously disease-free [7].

At Indiana University, our preferred approach for germ cell tumors in first relapse has been a single course of vinblastine plus ifosfamide plus cisplatin for cytoreduction followed by tandem transplant with HDCE [7].

Serum markers hCG or AFP are of pivotal importance in management and prognosis of patients with germ cell tumors and increased levels during chemotherapy are thought to represent viable residual disease [8]. A significant rise would seem to imply futility in continuing the same salvage chemotherapy regimen. Tumor marker rise at initiation of second course or within first week of second course of HDCE is also assumed to reflect a poor prognosis. To the best of our knowledge, there has been no published data on the incidence and significance of tumor marker rise during initiation of second course of HDCE. In this study, we have retrospectively analyzed the frequency and outcome of rising tumor marker at start of or within 1 week of initiation of second course of HDCE.

Patients and Methods

A single institution medical record review was conducted for 391 consecutive patients with germ cell tumors who underwent HDCE with peripheral blood stem cell rescue between February 1996 and December 2010. The Institutional Review Board at Indiana University approved the study.

Peripheral blood stem cells were collected prior to initiating high-dose chemotherapy. Stem cells were harvested after 5 days of mobilization with granulocyte colony stimulating factor 10 ug/kg subcutaneously. Daily apheresis was initiated and continued until 5×10^8 mononuclear cells/kg per cycle or 2×10^6 CD34+ cells had been collected. Patients received treatment either in the outpatient clinic or as inpatient. Two cycles of 700 mg/M^2 of carboplatin plus 750 mg/M^2 etoposide days both given intravenously 5, 4, and 3 days before infusion of peripheral blood stem cells. A minimum of 1 million CD34+ cells per kg was required for each cycle. Second cycle was administered after granulocyte and platelet recovery typically in 3 to 4 weeks. Weekly tumor markers were obtained.

The median age of patients was 29 years. Most patients had ECOG performance status 0 or 1. Twenty-five patients were noted to have rising hCG or AFP at initiation or within 1 week of second course of HDCE. Two patients had pure seminoma and the remaining 23 had NSGCT. Twelve patients were platinum refractory (progression within 4 weeks after treatment with standard dose cisplatin). Thirteen patients had hCG level ≥ 1,000 IU per liter and 8 patients had alphafetoprotein

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level ≥ 1,000 ng/liter at the initiation of HDCE. Patient characteristics are depicted in table 1.

Statistical Analyses

PFS was calculated from date of initiation of HDCE to date of progression or date of last follow-up. Overall survival was calculated from date of starting HDCE to date of death.

Results

A total of 391 patients have been treated with HDCE and peripheral blood stem cell rescue between February 1996 to December 2010. Twenty-five of 391 patients (6.4%) had marker rise at start or within 1 week of initiation of second course HDCE. If hCG or AFP was higher at start of second course compared to baseline, the second course of HDCE was not administered.

Fourteen patients were noted to have rising hCG (median rise 48.3 mIU/mL; range 3.2 to 8,863). Eleven patients developed rising AFP (median rise 18.3 ng/mL; range 4.2 to 1,018.8 ng/mL). Twenty-four out of 25 patients had a subsequent decline in the tumor marker with second course of HDCE.

With a median followup of 69 months (range 28-124), 7 out of 25 (28%) patients are continuously disease-free. In addition, 1 patient was lost to followup and was counted as a treatment failure. One patient was noted to have AFP rise 8 months after the transplant and was found to have reoccurrence with disease in abdomen and liver which was resected and patient was disease-free at last followup visit 12 months post-transplant. Another patient was noted to have AFP rise 3 months post-transplant and underwent exploratory laparotomy and remains disease-free 119 months post-transplant. Additionally, 1 patient had intermittent reoccurrences post-transplant, and underwent resections x 3 with chemotherapy including paclitaxel and gemcitabine. He stayed alive 151 months post-transplant. Thus, 10 of 25 (40%) are currently NED.

Prognostic score of 25 patients is described in table 2 below [7].

Characteristic	No. of Patients
No. of previous chemotherapy regimens	
2	13
≥ 3	12
Histologic type	
Seminoma	2
Non-seminomatous germ cell tumor	23
Initial IGCCCG Stage*	
Low risk	5
Intermediate risk	5
High risk	15
Platinum refractory	12
Serum hCG > 1000 IU/liter	13
Serum alpha-fetoprotein > 1000 ng/liter	8

*IGCCG – International Germ Cell Cancer Collaborative Group

Table 1: Characteristics of 25 Patients at the Beginning of High-Dose Chemotherapy.

Prognostic Score	No. of Patients
Low (0)	4
Intermediate (2 to 3)	6
High (4 to 7)	15

Table 2: Third-line or subsequent chemotherapy 3 points, platinum-refractory disease 2 points, IGCCCG high-risk stage 2 points [7].

Discussion

Relapsed or refractory testes cancer is a heterogeneous disease with overall survival ranging from 30% to 90% with HDCE followed by peripheral stem cell rescue depending on clinical characteristics [7,9]. Several adverse prognostic factors have been identified for patients undergoing salvage therapy with HDCE. Einhorn et al. has reported 3-variable model to predict overall survival after HDCE in 183 patients, defined by timing of high-dose chemotherapy, platinum sensitivity, or refractoriness, and International Germ Cell Cancer Collaborative Group (IGCCCG) score [7]. The International Prognostic Factors Study Group has also reported 5 independent prognostic parameters to define 5 prognostic categories in relapsed or refractory germ cell tumors [9]. These 5 prognostic parameters were primary site of disease, response to first-line treatment, progression-free interval, levels of AFP and hCG and liver/bone/brain metastases [9].

Tumor marker rise at or during the first week of second course of HDCE has never been studied previously. At Indiana University, if the marker rise at initiation of second course of chemotherapy is higher than the baseline levels, that patient will not undergo the second course due to significant progressive disease and it is felt continuing same HDCE would be futile. At our institution, 25 patients with marker rise, but still below baseline level, continued with second course of HDCE. Seven out of 25 patients are continuously disease-free with median followup of 69 months with range 28 to 129 months. Tumor marker rise during HDCE is most likely an independent adverse prognostic variable, but cure is still possible in this clinical setting.

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