Original Study

Clinical Outcomes of Metastatic Poor Prognosis Germ Cell Tumors: Current Perspective From a Referral Center

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Abstract

In this retrospective study, patients with poor-prognosis germ cell tumors (GCT) treated from a single referral center demonstrated high survival estimates that were stable through the years. Indeed, the major clinical implication is that using the available prognostic classification of metastatic GCT cannot allow the recognition of patients with a true chemoresistant disease. Moreover, the prognostic effect of treating patients with disseminated disease in referral centers should be further assessed.

Background: Survival estimates with first-line treatment for patients with metastatic poor prognosis germ cell tumors (GCT) are still suboptimal in the literature. We conducted a retrospective study to evaluate the outcome of patients referred to our tertiary cancer center. **Patients and Methods:** A retrospective analysis was conducted on patients who received at least first-line chemotherapy at our center. Distribution of clinical characteristics was evaluated in the periods $<$ 1997, 1997 to 2001, 2001 to 2006, and 2007 to 2013. The Kaplan–Meier method was used to estimate progression-free (PFS) and overall survival (OS). Univariable and multivariable Cox models with prespecified clinical variables were undertaken for PFS and OS. All tests and confidence intervals were 2-sided and set at a $P = .05$ level of significance. **Results:** Between 1982 and 2013, 168 patients were identified. The median age was 27 years (interquartile range [IQR], 22-34). The presence of liver, bone, or brain metastases trended to greater incidence from 1997 onward (27.5% $<$ 1997 to 55.6% in 2007-2013; χ^2 $P = .054$). Median follow-up was 102 (IQR, 63-166) months. Global 5-year PFS was 48.5% (95% confidence interval [CI], 41.5-56.8) and OS was 63.2% (95% CI, 56.0-71.2). In multivariable analysis, treatment period was not significantly associated with either PFS (overall $P = .229$) or OS (overall $P = .216$). **Conclusion:** In this single-center series of consecutive poor prognosis GCT we could observe greater PFS and OS than the historical estimates. This observation was independent from the period of treatment. Based on the present results, studies focused on improving the outcome in the sole poor-risk cohort should be discouraged. Results were biased by their retrospective quality.

Clinical Genitourinary Cancer, Vol. ■, No. ■, 1-7
Keywords: Chemotherapy, Germ cell tumor, Poor Prognosis, Survival, Testicular cancer

Introduction

Despite the global high cure rate for germ cell tumors (GCT), there is a proportion of metastatic patients yielding a more aggressive disease and for whom advances in treatment are still needed. These patients were defined in the late 90s as having a poor prognosis according the consensus of the International Germ Cell

Presented in part, as a poster, at the annual meeting of the European Society for Medical Oncology (ESMO), Madrid, Spain, September 2014

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Submitted: Dec 6, 2014; Revised: Jan 25, 2015; Accepted: Feb 1, 2015

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.02.002

Cancer Collaborative Group (IGCCCG) and constituted a proportion of 16% of patients who presented with an advanced-stage disease.[1] Since 1987, the standard therapy for these patients is represented by 4 cycles of PEB (cisplatin, etoposide, and bleomycin) followed by surgical clearance of residual resectable disease.[2]

Many attempts have been undertaken in the past 2 to 3 decades to improve the outcome in this subgroup of patients, including the use of either double-dose cisplatin regimens, dose-dense schedules, or the use of VIP (etoposide, ifosfamide, and cisplatin).[3-8] All these efforts failed to improve results of PEB chemotherapy and were characterized by a higher rate of side effects, and 4 cycles of VIP is the only available alternative nowadays for patients with intermediate or poor prognosis GCT when preservation of pulmonary function is necessary. Moreover, attempts to improve the outcome by intensifying the doses of chemotherapy with the use of hematopoietic stem cell support failed to demonstrate a superiority over standard dose chemotherapy in the first-line setting. Yet, an increasing overall survival (OS) over time with the use of conventional-dose chemotherapy (CDCT) should be accounted for, primarily attributable to the improvements of treatment options for patients with relapsing disease.[9]

We analyzed our single-center experience with these patients, which represents the picture of a referral center for this disease, with the aim to recognize the contemporary hurdles when attempting to improve the outcomes in the framework of prospective clinical trials.

Patients and Methods

Patient Population

We retrospectively identified 168 consecutive patients with poor prognosis GCT who were treated between April 1982 and December 2013 at Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy. Eligibility required the absence of any treatment (including surgery) given elsewhere in the first-line setting, outside of orchiectomy or surgical biopsy. Data on the following patient, disease, and treatment characteristics were collected: site of primary tumor, type and level of increased markers at diagnosis (after orchiectomy), metastatic sites, and type of first-line chemotherapy (classified as either CDCT or high-dose chemotherapy [HDCT]). Disease progression was defined as an increasing size of nonteratomatous masses or increase of serum tumor marker (STM) levels. Surgical radicality was defined as the complete removal of any evident disease with normal/normalization of STM levels. The primary objective of the analysis was to evaluate the evolution of clinical outcomes (progression-free [PFS] and OS) over time and to dissect the independent contribution of the treatment period. The study was conducted after approval by the institutional review board (IRB) at Fondazione INT Milan, Italy.

Statistical Analysis

Patient, disease, and outcome characteristics were summarized using descriptive statistics. The coprimary clinical end points of interest were PFS and OS. PFS was defined as the time interval between initiation of chemotherapy and the occurrence of disease progression or death, whereas OS was defined as the time to death from any cause; observation times were censored at the date of last contact in event-free patients. Survival curves for both end points were estimated with the Kaplan–Meier method. The association between covariates and treatment period was evaluated using the χ^2 test, and Cox proportional hazard regression models were applied to investigate putative prognostic factors on PFS and OS. The main focus was on dissecting the effect of the period of treatment on the outcome, after adjusting for major factors. With this aim, comparable groups of patients were identified by categorizing the period as follows: before 1997 (reference), 1997 to 2001, 2002 to 2006, and 2007 to 2013. The following prespecified variables were selected: type of first-line chemotherapy, tumor primary site, presence of liver, bone, or brain metastases (LBB), and increased STM levels. For the sake of parsimony, an arbitrary cutoff of 1000 IU/L was chosen to dichotomize patients and include sufficient numbers to run regression analyses. The discrimination ability of the multivariable model was then quantified using the Harrell concordance index, using a bootstrap procedure to correct for overfitting (bias-corrected c-index). The analyses were carried out using SAS (SAS Institute Inc) and R software (*http://www.r-project.org*). The results were considered statistically significant whenever a 2-sided $P < .05$ was achieved.

Results

Patient, Disease, and Treatment Characteristics

Baseline patient and disease characteristics are shown in Table 1. Median age was 27 years (interquartile range [IQR], 22-34); there were 49 patients (29.2%) with primary mediastinal nonseminomas (PMNSGCT), and 73 patients (43.4%) had nonpulmonary visceral metastases. Conventional dose chemotherapy consisted of 4 cycles of cisplatin, bleomycin, and either etoposide (PEB; n = 131; 78%) or other regimens (n = 3). HDCT (n = 34; 20.2%) included the sequential schedule of a multicentric phase II Italian trial consisting of a single course of high-dose cyclophosphamide followed by CD34-positive cell harvest and 2 cycles of cisplatin and high-dose etoposide (1.2 g/m^2 each) preceding the administration of a single HDCT course with high-dose (HD)-carboplatin area under the curve 25 and stem-cell rescue.[10]

The distribution of clinical variables over the years is shown in Table 2. Most patients classified with a poor prognosis because of increased STM levels only (n = 48) were in the less recent years (χ^2 $P = .002$), and a trend toward a greater frequency of cases with LBB metastases was observed in the more recent years ($P = .054$). The influence of having conducted a clinical trial of HDCT in the first-line setting at our center,[10] and the growing evidence toward HDCT in the salvage setting were the reasons for the heterogeneous distribution of HDCT throughout the years ($P < .001$).

Long-Term Side Effects, Response, Survival, and Multivariable Analysis

No cases of second cancers or secondary leukemias were observed, and these were the only assessable late sequelae in this cohort. Thirteen patients (7.7%) attained a complete response (CR) to chemotherapy and 91 (54.2%) a disease-free status after chemotherapy and surgery. Of the 107 patients who received surgery, 34 (31.8%) yielded a viable cancer (ie, viable GCT or teratoma with somatic transformation), 27 (25.2%) teratoma, and 45 (42.0%) fibrosis and necrosis (1 patient with missing information). Postchemotherapy surgical resection was radical in 77 cases