Treatment and Clinical Outcomes of Patients with Teratoma with Somatic-Type Malignant Transformation: An International Collaboration

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Purpose: We assessed prognostic factors, treatments and outcomes in patients with teratoma with malignant transformation, a rare occurrence among germ cell tumors.

Materials and Methods: Data on patients diagnosed with teratoma with malignant transformation between June 1981 and August 2014 were collected across 5 referral centers. Chemotherapy was dichotomized as based on germ cell tumor or teratoma with malignant transformation. Cox analyses were done to evaluate prognostic factors of overall survival, the primary end point. Each factor was evaluated in a univariable model. Forward stepwise selection was used to construct an optimal model.

Results: Among 320 patients the tumor primary site was gonadal in 287 (89.7%), retroperitoneal in 17 (5.3%) and mediastinal in 16 (5%). Teratoma with malignant transformation and germ cell tumor were diagnosed concurrently in 130 patients (40.6%). A total of 49 patients (16.8%) initially presented with clinical stage I. The remaining patients were at good (123 or 42.3%), intermediate (42 or 14.4%) and poor (77 or 26.5%) risk for metastasis according to IGCCCG (International Germ Cell Cancer Collaborative Group). First line chemotherapy was given for germ cell tumor in 159 patients (49.7%), chemotherapy for teratoma with malignant transformation was performed in 14 (4.4%) and only surgery was done in 147 (45.9%). Median followup was 25.1 months (IQR 5.4–63.8). Five-year overall survival was 83.4% (95% CI 61.3 to 93.5) in patients with clinical stage I and it was also worse than expected in those with metastasis. On multivariable analyses nonprimitive neuroectodermal tumor histology (overall $p = 0.004$), gonadal primary tumor ($p = 0.005$) and fewer prior chemotherapy regimens ($p < 0.001$) were independent predictors of better overall survival. Chemotherapy was not independently prognostic.

Conclusions: Less heavily pretreated teratoma with malignant transformation with a gonadal primary tumor and nonprimitive neuroectodermal tumor histology appears to be associated with longer overall survival. Generally, teratoma with malignant transformation had a worse prognosis than germ cell tumor. Uncertainties persist regarding optimal chemotherapy.

Abbreviations and Acronyms

CSI = clinical stage I

GCT = germ cell tumor

OS = overall survival

PNET = primitive neuroectodermal tumor

RPLND = retroperitoneal lymph node dissection

TMT = teratoma with malignant transformation

Accepted for publication December 22, 2015.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by the Conquer Cancer Foundation of the American Society of Clinical Oncology Merit Award (PG).

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0022-5347/16/1961-0095/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.12.082
Vol. 196, 95-100, July 2016
Printed in U.S.A.

Key Words: testicular neoplasms; teratoma; cell transformation, neoplastic; neoplasms, germ cell and embryonal; drug therapy

TERATOMA with malignant transformation is a rare event that occurs in late stages of the histological differentiation of GCT.[1,2] It is defined as the development of somatic nongerm cell malignancies in GCT according to WHO.[3] It represents an intriguing phenomenon in pathology with first reports dating back to the 17th century.[4,5] While malignant transformation has generally been thought to originate in teratomatous components, data support an origin from the yolk sac tumor component.[6] The link between GCT and TMT is represented by the presence of i(12p) (isochromosome 12p) in most cases.[7]

TMT has been reported as a component of testicular and extragonadal GCT.[8] This entity is also characterized by poorer responsiveness to chemotherapy compared to GCT and consequently by worse survival estimates. While surgery has a pivotal role in determining the possibility of cure, to our knowledge the benefit of any systemic therapy added to the aggressive surgical approach is still unknown.

Almost all available studies are limited in numbers with discordant findings due to being underpowered, which prevented multivariate regression analyses. Therefore, we attempted to better define the prognostic features of TMT and analyze the role of chemotherapy in a multicenter retrospective study.

PATIENTS AND METHODS

Overall data were collected from 5 centers in the United States and Europe. Uniform data fields comprising baseline characteristics and pathology information, treatments and chemotherapy regimens were collected using an Excel® sheet after receiving approval from the ethics committee/internal review board at each participating center. Inclusion criteria for the current analysis were male gender, age 15 years or greater, a diagnosis of TMT at any time in the disease course of germ cell tumor and a gonadal or an extragonadal primary site. Available criteria to define TMT were used, including an invasive and expansile growth pattern of somatic malignant elements when the histology was consistent with nongerm cell malignancy.[2] The presence of a teratomatous component together with TMT was reported in each case when present. CSI was defined as disease confined to the testis without clinical, radiological or biochemical evidence of disease. GCT chemotherapy was defined as any recognized conventional dose, platinum based combination or high dose chemotherapy regimen for advanced GCT. TMT chemotherapy was defined as the administration of any agent alone or in combination regimens that is currently in use for specific nongerm cell histologies (ie doxorubicin for sarcoma or nonplatinum regimens) as well as any chemotherapy regimen that differed from those in use for GCT at each center. This judgment on the type of chemotherapy was requested from the senior investigator at each site.

Patient, disease and outcome characteristics were summarized using descriptive statistics with frequencies and percents for categorical variables, and the median and IQR for continuous variables. Associations between categorical variables were assessed by the chi-square test.

The primary objective of the analysis was to determine clinical prognostic factors in patients with TMT. The secondary objective was to assess the role of chemotherapy in this disease. OS, the primary clinical end point, was calculated from the date of TMT diagnosis until death of any cause. Survival curves were created using the Kaplan-Meier method and the log-rank test was used for comparisons across different categories. Cox regression analyses were done to evaluate potential prognostic factors for OS. Each factor was evaluated in a univariable model while forward stepwise selection was used to construct an optimal model. Proportional hazards were assessed through visual inspection of the survival plots. Discrimination ability of the regression model was assessed using the c-index (concordance statistic). All tests were 2-sided with $p \leq 0.05$ considered statistically significant.

RESULTS

Patient, Disease and Treatment Characteristics

We analyzed the records of 320 patients. Supplementary table 1 (http://jurology.com/) lists the characteristics of patients, disease and treatment received. Patients were diagnosed with TMT between June 1981 and August 2014 at a median age of 28 years (IQR 24–35). TMT was found in the primary tumor in 167 patients (52.9%). A total of 130 patients (40.6%) were contemporaneously diagnosed with GCT and TMT in the primary tumor. In 37 patients initial biopsy showed metastatic disease with GCT only or a clinical diagnosis with serum tumor markers and TMT in the primary tumor at postchemotherapy surgery. Of 49 patients (16.8%) who initially presented with CSI 14 were treated with orchiectomy alone and 28 underwent primary RPLND, which resulted in viable nodal TMT in 10 (35.7%). The distribution of transformed histologies was adenocarcinoma in 50 cases (15.7%), rhabdomyosarcoma in 43 (13.5%), sarcoma not otherwise specified in 74 (23.3%), other mixed histologies in 53 (16.7%) and PNET in 98 (30.8%). Time of diagnosis was significantly associated with histology ($p < 0.001$, fig. 1).