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Prognostic factors of metastatic testicular non-seminomatous germ cell tumors after chemotherapy

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ABSTRACT

Background: We evaluated the prognostic factors of metastatic testicular non-seminomatous germ cell tumor (NSGCT) after chemotherapy.
Materials and methods: Data from 20 metastatic testicular NSGCT patients were retrospectively collected between January 2002 and December 2015. The evaluation of prognostic factors included age, pulmonary metastasis, cancer stage, International Germ Cell Cancer Collaborative Group (IGCCCG) classification, and histology.
Results: Twelve (60%) and eight (40%) patients had stage 2 and 3 disease, respectively. Good, intermediate, and poor prognoses were ten, six, and four patients, respectively. Eight patients (40%) were aged above 30 years at detection of testicular; cancer, and seven patients (35%) had pulmonary metastases. Sixteen patients had mixed germ cell tumors (MGCTs) only, Four were unfavorable histology (two MGCTs with choriocarcinoma-predominant, one pure choriocarcinoma and MGCTs with embryonal rhabdomyosarcoma transformation). Thirteen patients (65%) showed no evidence of disease (NED), and 7 patients (35%) that did not survive post therapy. Pulmonary metastases ($P = 0.02$), unfavorable histology ($P = 0.007$) were found to be prognostic factors of NED in patients with metastatic testicular NSGCTs. Age ($P = 0.06$) and stage ($P = 0.06$) showed considerable trend of significance. But risk group of IGCCCG exhibited no significant difference ($P = 1$).
Conclusion: The presence of pulmonary metastases, and unfavorable histology but not GCCCG classification were associated with poor prognosis in in patients with metastatic testicular NSGCTs. Prognostic reclassification for IGCCCG groups is suggested from our study.

1. Introduction

Testicular germ cell tumors are subdivided into seminomas and non-seminomas. Metastatic non-seminomatous germ cell tumors (NSGCTs) can be cured with chemotherapy and/or surgical management.[1] The International Germ Cell Cancer Collaborative Group (IGCCCG) classification has been used since 1997 to classify metastatic germ cell tumors (GCTs) based on prognosis, and the reported five-year overall survival rates were 91% in good-risk groups, 79% in intermediate-risk groups, and 48% in poor-risk groups.[2,3] Shintaku et al. reported that overall survival for patients with metastatic NSGCTs was improving across all risk groups, with a particularly large increase in survival among patients with a poor prognosis in Japan.[4] However, IGCCCG classification based-prognoses need to be updated to remain applicable, especially for intermediate- and poor-risk NSGCTs.[5–7]

Here, we retrospectively evaluated the prognostic factors of metastatic non-seminomatous germ cell tumor (NSGCT) after

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chemotherapy. Patient treatment is also discussed.

2. Materials and methods

2.1. Study population

We conducted a retrospective case series study using data collected from patients admitted to the oncology wards of Chang-Gung Memorial Hospital, Taoyuan, Taiwan, between January 2002 and December 2015. The majority of data were provided by a single physician, who was an expert on urological malignancies. Twenty patients with metastatic testicular NSGCTs were recruited. Diagnosis and evaluation of tumor progression was based on histology, the tumor markers alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (β-HCG) and computed tomography (CT) scan findings. Testicular cancer was staged as follows according to the American Joint Committee on Cancer (AJCC), 7th edition[8]: Stage II was defined as the spread of cancer beyond the testis and involvement of the retroperitoneal lymph nodes and Stage III was defined as the spread of cancer beyond the supradiaphragmatic lymph nodes, with metastasis to the lung, liver, bone, and brain. Patients were alive and presented with no evidence of disease (NED), and were classified according to the IGCCCG into good-, intermediate-, and poor-risk groups based on AFP, β-HCG, and lactic dehydrogenase (LDH) levels.[2] The good-risk group had AFP levels < 1000 ng/ml, β HCG levels < 5000 mIU/ml, and LDH levels < 1.5 times the ULN (upper limit of normal); the intermediate-risk group had AFP levels between 1000 and 10,000 ng/ml; β-HCG levels between 5000 and 50,000 mIU/ml iμ/ml, and LDH levels 1.5–10 times the ULN; and the poor-risk group had AFP levels > 10,000 ng/ml, β-HCG > 50,000 mIU/ml miμ/m, and LDH levels > 10 times the ULN, or non-pulmonary visceral metastasis (e.g., liver, bone, and brain metastasis).

Initial chemotherapy consisted of four courses of bleomycin, etoposide, and cisplatin (BEP) chemotherapy. Retroperitoneal lymph node dissection was suggested when residual radiographic abnormalities were present after chemotherapy. Patients presenting with residual tumors were given two courses of BEP or etoposide and cisplatin (EP) as salvage chemotherapy. Four courses of etoposide, ifosfamide, and cisplatin (VIP) was provided as second-line chemotherapy in the event of tumor recurrence. For patient safety, BEP, EP, and VIP chemotherapy were given with modified dosages under hospitalization. The chemotherapy regimens used were as follows: for BEP, bleomycin (15 U), etoposide (100 mg/m^2), and cisplatin (30 mg/m^2) were intravenously administered on days 1, 2, and 3, repeated every 21 days; for EP, etoposide (100 mg/m^2) and cisplatin (30 mg/m^2) were intravenously administered on days 1, 2, and 3, repeated every 21 days; for dosage of VIP, ifosfamide (2 gm), mesna (400 mg x 5 doses), etoposide (100 mg/m^2), and cisplatin (30 mg/m^2) were intravenously administered on days 1,2, and 3, repeated every 21 days.

High remission rates can be achieved when treating testicular NSGCTs and few patients relapse following therapy. NED was defined as at least two years post-chemotherapy, and prognostic parameters of NED, including age, pulmonary metastases, cancer stage, IGCCCG classification, and unfavorable histology (pure choriocarcinoma or MGCTs with choriocarcinoma-predominant or sarcomatous malignant transformation) were analyzed.

2.2. Statistical methods

We used the Fisher's Exact test due to small sample size to detect differences between subgroups, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients' characteristics

We recruited 20 consecutive cancer patients with metastatic testicular NSGCC, collected. Tables 1 and 2 show the clinical characteristics of each NED of 13 patients (65%) and 7 patients (35%) that did not survive post therapy, respectively. Patient age ranged 19–55 years old, with a median age of 25 years. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Three patients had testes that were undescended from the inguinal canal. Case 7 had previous orchiopexy. Histology indicated MGCTs only in 16 patients: two patients (Cases 18 and 19) had MGCTs, but with predominant choriocarcinoma; Case 18 had a retroperitoneum choriocarcinoma from a burned-out testicular tumor. Case 17 had a MGCT, with malignant transformation into embryonal rhabdomyosarcoma; and Case 20 had a pure choriocarcinoma. Initially, all patients had retroperitoneal mass or lymph node metastases, and seven had pulmonary metastases. Other metastatic sites included the supraclavicular lymph nodes (n = 2), liver (n = 1), bone (n = 1), and skin (n = 1).

Twelve (60%) and eight (40%) patients had stage 2 and 3 metastatic testicular NSGCTs, respectively. The IGCCCG risk classifications were good in 10 patients (50%), intermediate in six (30%), and poor in four (20%).

3.2. Treatment

3.2.1. Orchiectomy and chemotherapy

Eighteen cases received unilateral radical orchiectomy. Two patients had testicular tumors arising from the inguinal canal; one of these patients received an incomplete tumor resection, while the other only received a tumor biopsy. All 20 patients received four courses of chemotherapy after orchiectomy and pathological confirmation of disease.

Cases in Table 1 showed complete tumor disappearance after chemotherapy without retroperitoneal lymph nodes dissection was achieved in eight cases. Two cases (cases 10 and 12) experienced metastatic recurrence 8 and 6 months after chemotherapy, respectively, Two cases (Cases 15 and 16) in Table 2 showed tumor regression after chemotherapy without retroperitoneal lymph nodes dissection.

Case 15 initially had normal levels of the tumor markers AFP and β-HCG, but six months later experienced recurrent multiple pulmonary metastases with elevated AFP (588 ng/ml). He received VIP chemotherapy, but died of disease progression, with a survival time of 25 months.

Case 16 had initial retroperitoneal, pulmonary, and skin metastases, with serum AFP and β-HCG levels at 396 ng/ml and 2630 mIU/ml, respectively; nine years later, he experienced retroperitoneal and pulmonary recurrence, with rapidly rising β-HCG levels. He received and initially responded to EP and VIP chemotherapy, but disease progression (particularly lung and brain metastases) occurred. He died of disease progression 28 months later, with a survival time of 136 months. His β-HCG level at death reached 272,675 mIU/ml.

3.2.2. Residual lesions with retroperitoneal lymph node dissection and lung metastasectomy

Seven cases in Table 1 had residual lesions over the retroperitoneum. Of these, five received retroperitoneal lymph node dissection; pathology showed teratoma in two (Cases 2 and 8) and malignant cells in two (Cases 1 and 11) each. One patient (Case 6) was negative for malignant cells.

Cases 2 and 8 had teratoma cases did not receive further

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