New research in testicular cancer, ASCO-GU 2017

Robert J. Hamilton, MD[1]; Christian Kollmansberger, MD[2]

[1]University of Toronto, Toronto, ON; [2]University of British Columbia, Vancouver, BC; Canada

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Adjuvant therapy

At the American Society of Clinical Oncology 2017 Genitourinary Cancers Symposium, researchers presented the results of a single-arm trial investigating the efficacy of a single cycle of bleomycin, etoposide, and cisplatin (BEP) as adjuvant chemotherapy for high-risk, stage 1, non-seminomatous or combined germ cell tumours of the testis (NSGCTT).[1] The 236 subjects received one cycle of BEP, with etoposide dosed at 165mg/m^2 Day 1–3 and cisplatin 50 mg/m^2 Days 1 and 2. They were followed for five years post-orchiectomy. The primary efficacy endpoint was malignant recurrence at two years, defined as active undifferentiated disease ± rising markers, multiple site relapse. Teratoma differentiated recurrence was a secondary endpoint.

Acute Grade 3/4 toxicities included: neutropenia in 75 patients (32.2%), leukopenia in 38 (16.3%), and febrile neutropenia in 15 (6.4%). Delayed toxicities (6–24 months post-cycle) were rare, with three Grade 3 and three Grade 4 toxicities reported.

The four-year malignant recurrence rate was 1.8% and including teratoma, the overall recurrence rate was 3.1% (Fig. 1). Overall survival (OS) at two years was 99% (234/236 still alive).

The investigators concluded that the recurrence rate with a single BE500P cycle was similar to that seen in previous trials with BE360P x two cycles. The single-cycle regimen would reduce overall chemotherapeutic exposure in this young patient group, but must be weighed against active surveillance (AS) where the majority of patients will not receive any chemotherapy.

High-dose chemotherapy for relapsed germ cell tumours

Researchers presented the results of a phase 2 trial of paclitaxel (T) plus ifosfamide (I) followed by high-dose carboplatin (C) plus etoposide (E) with stem-cell support (TICE) among 101 patients with relapsed advanced germ cell tumours (GCTs–71 with testicular tumours).[2] Carboplatin levels were measured on Days 1 and 2 with the hypothesis that the Day 3 carboplatin dose could be optimized to reach target (area under the curve [AUC] 24 mg/min/ml). The primary endpoint was complete response rate to chemotherapy ± surgery.

Seventy-nine patients were evaluable for efficacy. Day 3 carboplatin dose modifications ranged from -33% to +44%. The rate of complete response was 45% (17% with chemotherapy alone, 28% with chemotherapy plus surgery) (Table 1). A further 25% had a partial response with negative markers for an overall favourable response rate of 70%. Median progression-free survival (PFS) was 12.3 months. There were 40 deaths overall, with a median OS of 33.9 months.

There was one death related to treatment (sepsis) and 41 Grade 3/4 toxicities were noted, most being gastrointestinal. The investigators concluded that carboplatin drug monitoring should become routine practice for salvage regimens involving high-dose carboplatin. Due to the small patient population and the lack of randomized comparator arm, only limited conclusions can be drawn from this study and carboplatin monitoring needs further evaluation in larger trials. Based on the results of this trial, active drug monitoring for carboplatin is an option.

Liver metastases in GCTs

British investigators retrospectively identified 36 patients (34 NSGCT) with metastatic GCT to the liver and evaluated their responses to therapy.[3] Twenty patients received the standard protocol of BEP every 21 days; 15 patients received actinomycin-D, high-dose methotrexate, etoposide, and cisplatin (GAMEC) every 14 days; and one patient received cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, etoposide (POMB/ACE) chemotherapy. Twenty patients had an induction cycle of cisplatin, vincristine and bleomycin (Baby-BOP) prior to initial treatment.

Twelve (33%) patients had a complete response and 19 (53%) had radiologic partial response in the liver. Only five patients underwent liver resection, none had viable GCT. Too few patients underwent retroperitoneal lymph node dis-

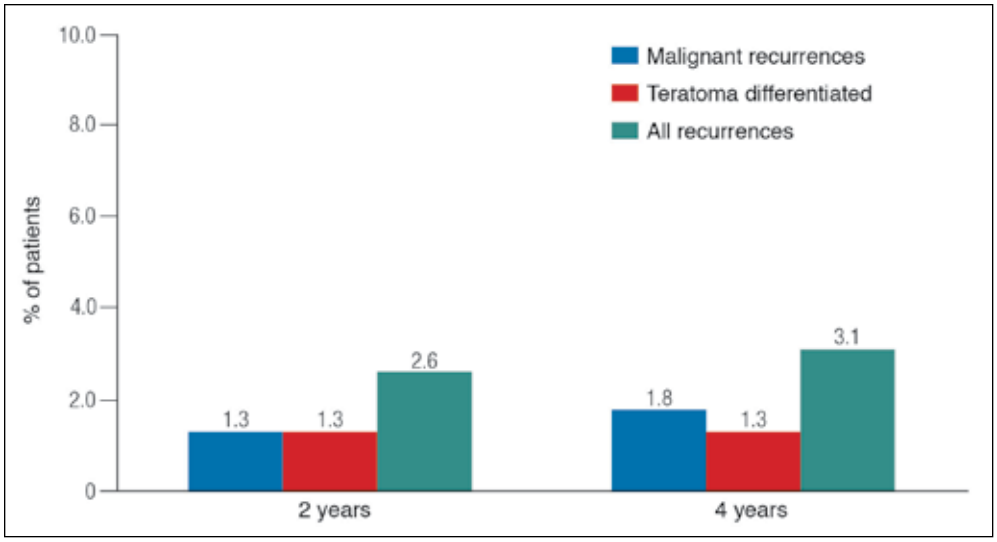

Fig. 1. Recurrence rates over two and four years with one cycle of adjuvant bleomycin, etoposide and cisplatin (BEP) for non-seminomatous or combined germ cell tumours of the testis (NSGCTT).

section (RPLND) and liver resection to make conclusions about concordance of histology. The authors concluded that overall response of liver metastases to chemotherapy was favourable, with any progression events occurring at extra-hepatic sites. They questioned whether there was a role for liver resection after chemotherapy if the initial response to chemotherapy was favourable. Patients with liver metastases appear to have a good response to chemotherapy. The best management of patients with liver metastases remains to be conclusively addressed. Until proven otherwise, resection of residual lesions in the liver should be considered.

Predictors of malignant tissue in residual masses after chemotherapy before surgery for NSGCT

In a retrospective study of 193 patients with NSGCT undergoing neoadjuvant chemotherapy, French investigators identified predictors of malignant tissue in residual masses.[4] By multivariate analysis, the only predictors were size of residual mass and pre-chemotherapy alpha-fetoprotein level greater than the upper limit of normal. The model performed only modestly, with an AUC of 0.71, and only 0.59 in the validation set (n=98). The predictive variables identified in this study have been identified in other studies. In fact, these variables are a subset of the larger Vergouwe model, which has been validated in several cohorts and performs better with AUCs over 0.80. Given the modest discrimination and accuracy of any prediction model, including the one reported here, resection of residual lesions remains the standard of care for metastatic non-seminoma.

Table 1. Responses to high-dose TI-CE chemotherapy regimen in patients with relapsed germ cell tumours (n=79 patients)

Response	n	%	Combined %	
CR (chemotherapy alone)	13	17%	45% CR	70% Favourable response
CR (chemotherapy + surgery)	22	28%		
Partial response with negative markers	20	25%		

CR: complete response; TI-CE: paclitaxel [T] plus ifosfamide [I] followed by high-dose carboplatin [C] plus etoposide [E].

Ultrasound for followup of patients with GCTs

A retrospective study of 203 patients with Stage I NSGCT were categorized into two groups: Group 1 – followed by computed tomography (CT) for three years, then abdominopelvic ultrasound (n=80); Group 2 – followed by CT for the entirety of their surveillance (n=123).[5] Median followup was 6.7 years in Group 1 and 8.1 years in Group 2. After the third year of surveillance, only five relapses were noted in the whole cohort (one in Group 1; four in Group 2). The authors concluded replacing CT with ultrasound appeared safe after the third year of Stage I NSGCT surveillance; however, caution is needed — this study is underpowered, retrospective, and only evaluated ultrasound in the time period after which most of the NSGCT relapses have occurred. Further studies investigating the optional followup schedule and diagnostic method are needed. In the interim, CT scanning remains the gold standard for GCT patients.

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