Germ cell tumours such as testicular cancer typically affect adolescent and young adult males. Since the introduction of cisplatin, outcomes for patients with advanced germ cell tumours have improved with cure rates exceeding 80% overall. However, outcomes are considerably worse for patients with intermediate or poor prognostic features with cure rates of only 79% and 48%, respectively [1].

We previously reported a single-arm, multicentre, open-label, phase II trial (Australian New Zealand Clinical Trials Registry: ACTRN1260700294459) of 43 patients with metastatic germ cell tumours [2]. They were treated using an accelerated regimen of first-line bleomycin, etoposide, and cisplatin (BEP) chemotherapy by cycling 2-weekly rather than the standard of 3-weekly cycles. The primary end point of feasibility was met, with 86% of patients able to complete the etoposide and cisplatin components of BEP and be eligible to receive a fourth cycle of BEP by day 50, i.e. with a delay of no more than 7 days. Efficacy appeared promising. We now present long-term efficacy outcomes after over 5 years of median follow-up.

Eligibility and study procedures have been described in detail in the main study report [2]. In brief, patients were eligible if they had metastatic germ cell tumours arising in the testis, retroperitoneum, mediastinum, or ovary of any International Germ Cell Cancer Collaborative Group (IGCCC) prognostic group and if they had radiologically measurable disease. Patients received cisplatin 20 mg/m² on days 1, 2, 3, 4, and 5; etoposide 100 mg/m² on days 1, 2, 3, 4, and 5; and pegylated G-CSF 6 mg on day 6, all repeated every 2 weeks for four cycles (or three cycles for good-risk patients). Bleomycin was given at 30 kIU weekly to a total 12 doses (9 doses for good risk).

Forty-three eligible patients were enrolled between February 2008 and November 2010. According to the IGCCCG prognostic group, 12 had poor-risk disease, 16 intermediate-risk disease, and 15 good-risk disease. With a data cut-off date of 1 November 2015, the median follow-up was 6.2 years (inter-quartile range: 5.7–6.5) for survival and 6.2 years (inter-quartile range: 5.7–6.4) for relapse. Eight of 43 patients relapsed; 2 relapses occurred within 3 months of enrolment (refractory disease), 6 relapses occurred between 3 and 15 months (early relapse), and no late relapses occurred. Three of 43 patients died. All had experienced disease relapse; however, one patient had a complete response to second-line treatment and died due to an unrelated malignancy (secondary to Li Fraumeni syndrome). The 5-year progression-free survival was 50% [95% confidence interval (CI) 21% to 74%] for poor-prognosis, 94% (95% CI 65% to 99%) for intermediate-prognosis, and 93% (95% CI 61% to 99%) for good-prognosis patients. The 5-year overall survival was 92% (95% CI 54% to 99%) for poor-prognosis, 94% (95% CI 63% to 99%) for intermediate-prognosis, and 100% (95% CI NA) for good-prognosis patients.

In summary, the long-term efficacy data of accelerated BEP in this phase II trial remain promising. This trial and a similar UK study [3] provide the rationale for a currently recruiting Australian-led international randomised phase III trial comparing accelerated versus standard BEP chemotherapy (Australian New Zealand Clinical Trials Registry: ACTRN12613000496718).

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funding

This work was supported by the Cancer Council New South Wales, Cancer Council Victoria, Cancer Council Queensland, and Cancer Council South Australia (Grant number 512329, 2008–10). The Australian and New Zealand Urogenital and Prostate Cancer Trials Group is supported by Cancer Australia and Cancer Institute New South Wales.

disclosure

The authors have declared no conflicts of interest.
Reply to the letter to the editor ‘the clinical dilemma of grade 3 follicular lymphoma’ by Sorigue et al.

As pointed out by Sorigue et al. [1] in their letter related to our work [2], follicular lymphoma (FL) grade 3A and 3B is managed in Europe to some extent differently to China and the United States. In their letter, Sorigue et al. emphasize that this setting of clinical borders is not evidence-based. We agree with this comment and like to add that these treatment recommendations were developed from historical classifications before the WHO classification in 2001 implemented grading of FL. Historically, the Kiel classification used in many European countries at that time put emphasis on cellular differentiation (centroblasts versus centrocytes), while the Rappaport classification and the Working Formulation predominantly used in the United States defined the (follicular) growth pattern as the overriding classification criterion. Clinical care followed the pathological classification. Certainly, deeper insight into the molecular pathogenesis using new diagnostic tools will identify true biological subgroups. At the time being, our data illustrate that FL grade 3A and 3B are rather rare variants and patients harbor FL of various grades; these FL subtypes can show overlapping immunophenotypic and genetic features (Figure 1) [2, 3]. Strikingly, FL3A and FL3B virtually never coexist [2]. From our point of view, these co-existence pattern of FL grades are very relevant for the definition of arbitrary subgroups since they indicate pathogenetical relation (in analogy to ‘grey zone lymphoma’) [4] and lumping according to these pattern might reduce inter-observer variability [2]. Following the concept of co-existence pattern, FL grade 1/2 and 3A might be joined in one arbitrary group. This seems to be ‘a step back’ in time rather than advancement in lymphoma classification. However, with the available evidence, it remains questionable whether grading of FL according to current guidelines identifies prognostic subgroups of FL, although our results suggest that some FL grade 3A might have a superior outcome to FL grade 1/2. Potentially curable FL subgroups can be defined by clinico-pathological characteristics of FL such as localization, dissemination pattern, grade, and presence of BCL2 translocations exemplified by localized variants of FL in skin, testis, and duodenum as well as a ‘pediatric type’ of FL [2, 5, 6]. Future developments might make the clinical dilemma described by Sorigue et al. even more apparent. Due to differences in molecular pathways targeted either in FL 1/2 or DLBCL, treatment recommendations for FL and DLBCL will diverge in the future. This development will also alter therapy of rare entities such as FL grade 3A and 3B which are ‘linked’ to these large entities. We agree with Sorigue et al. in emphasizing the need to complement the currently available evidence on diagnosis, biology, prognosis, and treatment of FL grade 3 with future research that hopefully will ultimately determine how we need to identify subgroups and treat FL in the future. A conceivable future scenario might in fact be that subtle morphological subtyping becomes dispensable since solely the presence of molecular targets will determine what subgroups need to be identified.