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Comments and Critique

Continued Refinement in the Treatment of Germ Cell Tumour Patients

THE TREATMENT of metastatic non-seminomatous germ cell tumours (NSGCT) has enjoyed considerable success since the introduction of cisplatin-based chemotherapy. Major advances include standardisation of the cisplatin dose, deletion of maintenance therapy, reduction of the duration of treatment and the number of drugs, and the substitution of etoposide for vinblastine in the majority of treatment regimens. Concepts which evolved during the 1980s and are now standard are underscored by three articles in this issue. Dearnaley *et al.* (p. 684) report long-term follow-up of NSCGT patients and the relationship of prognosis to tumour bulk and serum tumour markers, thereby addressing the issue of risk assignment. Harland *et al.* (p. 691) report the results of therapy with etoposide plus bleomycin and carboplatin, the less toxic cisplatin analogue, with dosing determined by the patient's glomerular filtration rate. Jansen *et al.* (p. 695) report the long-term follow-up of patients with postchemotherapy surgery for residual disease illustrating the necessity of adjunctive surgery after chemotherapy and the predictive value of the pathological findings. These papers address different aspects of NSGCT treatment which concern the maintenance of efficacy and reduction of toxicity in patients with good risk disease and improvement of efficacy with tolerable toxicity in patients with a poor prognosis.

A common definition of good and poor risk remains elusive but reasonable accuracy can be achieved. Only in good risk patients is toxicity reduction a reasonable endpoint. The study by Dearnaley *et al.* evaluated 127 men with metastatic NSGCT treated with cisplatin, etoposide and bleomycin (BEP). The 5-year survival was 87%. This study confirms the previous observation of the Medical Research Council that the treatment outcome of NSGCT patients is related to the pretreatment tumour bulk and the level of the serum tumour markers. The majority of patients (90/127) had small volume disease and 88/90 (97.8%) were disease-free at 5 years. Patients with either "large" or "very large" volume disease had a survival of 72% and 27%, respectively. Patients with low marker values had a 5-year survival of 91% vs. 66% for patients with high marker values. Using these criteria, NSGCT patients are prospectively assigned to either good risk trials, the objective of which is to reduce the toxicity and maintain efficacy of chemotherapy, or to poor risk trials, the primary objective of which is to improve survival with tolerable toxicity. The substitution of cisplatin by carboplatin is being evaluated in good risk patients; poor risk patients are randomised to receive either the now standard BEP or the more toxic bleomycin, vincristine, cisplatin-etoposide, ifosfamide, cisplatin (BOP-VIP) regimen to assess for enhanced efficacy.

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The concept of risk assignment is valid and must be preserved in the interest of patient care but caution must be taken not to enter good risk patients in poor risk trials. A number of clinical factors in NSGCT patients are now routinely used by various groups to allocate patients to good and poor risk trials. Tumour bulk or extent of disease and the pretreatment values of serum tumour markers are independent, significant prognostic factors in the majority of studies. Logically, poor risk patients should constitute the 20–30% of patients who will fail initial therapy or relapse and die of their disease. However, lenient eligibility criteria for poor risk trials that attempt to capture all potential treatment failures can assign a high proportion of all NSGCT patients with metastatic disease to poor risk trials. The end result is improvement in survival proportions of both the good risk and poor risk populations (a process termed stage migration) and exposure of good risk patients to unnecessary toxicity. This lack of consensus on the precise details of pretreatment characteristics that portend good and poor prognosis disease and the resulting variability of eligibility criteria can substantially influence trial results and make intertrial comparisons difficult at best [1]. International standard criteria for good and poor risk disease would be very useful.

Bleomycin-associated pulmonary and vascular toxicity are of particular concern in good risk patients [2, 3]. In the study by Dearnaley *et al.*, 13% of patients demonstrated symptomatic bleomycin pulmonary toxicity; 4 patients required corticosteroid administration and 1 patient died. The death from bleomycin-induced pneumonitis was observed in a patient who received a cumulative bleomycin dose of only 180 mg. This level of toxicity is not unusual. In a randomised trial of 244 NSGCT patients comparing cisplatin, vinblastine and bleomycin (PVB) with BEP, 5 (2%) patients died of bleomycin pneumonitis [4]. This degree of toxicity must be avoided in the good risk patient population. Bleomycin is also implicated in the development of Raynaud's phenomenon. This complication was observed in 6% of patients in the randomised trial of PVB vs. BEP and was equal in both the etoposide and vinblastine containing arms [4]. Raynaud's phenomenon was not observed in patients treated with etoposide and cisplatin alone [5].

Limiting the use of bleomycin has been the objective of several trials in good risk patients. The two-drug regimen of etoposide and cisplatin in 84 good risk patients at Memorial Sloan-Kettering Cancer Center resulted in 87% disease-free survival at a median follow-up of 61 months [5, 6]. A randomised trial of cisplatin plus etoposide with or without bleomycin in good risk patients defined by the criteria of the EORTC is on-going and, in a preliminary analysis, the efficacy of both regimens is similar [7]. The Southwest Oncology Group compared PVB with vinblastine, cisplatin and etoposide and response pro-

portions, the frequency of relapse and overall survival were equivalent [8]. Toxicity was greater in the bleomycin-containing arms of these trials. Three cycles of BEP (cumulative bleomycin dose of 270 mg) in good risk patients by Indiana University criteria achieved 92% disease-free survival which was equivalent to that observed in patients receiving four cycles of therapy [9]. Unfortunately, no toxicity data were provided. In good risk patients, bleomycin appears to add toxicity without enhanced survival benefit. Deleting bleomycin in patients receiving four cycles of therapy or limiting the cumulative dose of bleomycin to three cycles of therapy will reduce the incidence of this potentially lethal toxicity.

Reduction of toxicity may be possible with the use of carboplatin which causes less emesis, nephrotoxicity and ototoxicity than cisplatin. Harland *et al.* report the results of treatment with etoposide, bleomycin and carboplatin. The dose of carboplatin is adjusted for the patient's glomerular filtration rate rather than the body surface area. This modification targets a predetermined area under the curve (AUC) that maximises antitumour efficacy and minimises myelosuppression. A prospective evaluation of this dosing methodology is ongoing. The substitution of carboplatin for cisplatin in the BEP regimen is feasible and appears effective [10–12]. However, the definitive substitution of carboplatin for cisplatin awaits the completion of randomised trials such as that in good risk patients at Memorial Sloan-Kettering Cancer Center comparing two-drug therapy with carboplatin and etoposide vs. cisplatin and etoposide.

The study by Jansen *et al.* reports long-term results of 102 patients who underwent surgical resection of residual disease after chemotherapy. 88% of the patients with residual mature teratoma enjoyed long term disease-free survival vs. 59% of patients with residual carcinoma. This study confirms prior reports of the necessity for surgical resection of residual disease in patients who have undergone chemotherapy for metastatic disease and the survival statistics of patients with resection of residual viable carcinoma [3–16]. Despite the morbidity of ejaculatory dysfunction and sterility with adjunctive surgery, no standard criteria currently exist which can correctly select patients in whom postchemotherapy surgery can be avoided. One study recommended observation for patients in whom no evidence of teratoma was found in the primary lesion and the volume of the retroperitoneal mass after the chemotherapy had decreased by 90% or more [17]. However, in a separate study examining this same issue, Toner *et al.* found that 8/39 (21%) patients with residual retroperitoneal masses of up to 1.5 cm in maximal diameter had viable malignancy (3 patients) or mature teratoma (5 patients) [16]. The absence of teratoma in the primary specimen did not preclude the finding of teratoma in the resected specimen since 33% of 75 patients without teratoma in the primary tumour had teratoma in resected metastases. Resection of residual disease after chemotherapy remains necessary in the majority of patients with metastatic NSGCT.

In summary, the three papers by Dearnaley *et al.*, Harland *et al.* and Jansen *et al.* emphasise the proper management of germ cell tumour patients in the 1990s. The toxicity of chemotherapy in good risk patients should be minimised and the increased toxicity associated with intensive therapy can be limited to a minority of patients in whom the likelihood of long-term survival is low. Adjunctive surgery after chemotherapy is an integral part of the treatment of most NSGCT patients with metastatic disease. Standardisation of criteria for entry to good and poor risk NSGCT trials should be a goal of the 1990s. Post-treatment variables such as evidence of residual malignant disease in patients undergoing resection of residual abnormality after chemotherapy and patients in whom the decay of serum tumour markers is prolonged define a high risk population in which new approaches are required.

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