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Treatment of Refractory Testis Cancer: Salvage or Savage Chemotherapy?

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THE MANAGEMENT of testicular cancer is now regarded as the paradigm of treatment of the curable cancers, with apparent cure rates of greater than 70% for metastatic disease [1, 2]. Our increased understanding of the biology of germinal malignancy [3] has had clinical application in the use of tumour markers as monitors of clinical progress and as determinants of prognosis, in the development of more accurate and appropriate staging of the disease, the use of multimodality treatment programmes, and in the modification of treatment on the basis of anticipated prognosis.

The introduction of surgical resection of residual masses after the completion of induction chemotherapy has taught us much about the efficacy of chemotherapy for germinal malignancy. In the early reports of surgery after the use of the combination of cisplatin, vinblastine and bleomycin (PVB), equivalent proportions of patients had necrotic tissue, differentiated teratoma and viable cancer in the resected specimens [1, 2, 4]. These ratios have now changed; a much smaller percentage of specimens have residual cancer since the development of more intensive chemotherapy regimens for "poor risk" tumours, based upon various systems of prognostication.

PROGNOSTIC FACTORS

The prediction of prognosis for metastatic germ cell tumours remains a controversial issue [2, 5–9]. Although there is general agreement that a significantly worse outcome from "conventional" chemotherapy (such as PVB) is achieved for patients with very large volume tumours, those with very high levels of circulating tumour markers, and those with extragonadal germ cell tumours, there is no consensus regarding the arbitrary cut-off levels for "large" tumour volume and "high" levels of tumour markers. Furthermore, the prognostic significance of hepatic, osseous or brain metastases, serum lactate dehydrogenase levels, histological subtypes and numbers of metastases remain controversial [2, 5–9]. It has thus been difficult to compare outcomes of treatment for so-called "poor risk" tumours.

Similarly, the analysis of outcomes of "salvage" treatment has been made difficult by such factors as the variation in the selection of drugs and in the dose-intensity of initial chemotherapeutic programmes and whether the intensity of primary treatment has been adapted on the basis of documented adverse prognostic determinants. Furthermore, the actual definition of relapse has been quite varied, with some series including unbiopsied residual or recurrent masses after chemotherapy (with negative tumour markers) or so-called "unresectable" residual masses (without any definition of the experience of the surgeon in this rigorous procedure nor of the adequacy of the attempt to resect the tumour). In addition, patients with "marker only" relapses are likely to constitute a very different entity from those with large volume relapsed disease, with added impact from the range of additional prognostic determinants discussed above.

Clearly, the outcomes of salvage programmes with more stringent criteria of entry are likely to appear superficially less impressive than those reported by investigators with a more inclusive approach. Nevertheless, we have attempted to assess critically the current approaches to the management of tumours that have relapsed after initial therapy.

NEW STRATEGIES OF TREATMENT

Several strategies have been potentially available for the treatment of relapsed/failed germ cell tumours: (i) more intensive regimens, predicated on increased drug dosage, increased frequency of delivery or both, with the ultimate attainment of increased dose intensity; (ii) new agents, based on new mechanisms of action or reduced patterns of toxicity (in turn facilitating the use of higher doses); (iii) non-crossresistant schedules, in which there is an attempt to overcome patterns of resistance by the concurrent or sequential use of agents that act by different mechanisms; (iv) strategies designed to protect normal tissues, allowing the administration of higher doses of treatment; and (v) biochemical modulation or other pharmacological approaches to overcome known patterns of resistance to treatment.

For the management of germ cell tumours, some of these broad strategies have been combined into complex regimens, as summarised below, while others have yet to be assessed. Due to the relative infrequency of failure of primary treatment of germ cell tumours, the numbers of patients treated with salvage regimens have been small, and the trials reported to date have been of the phase I–II design, without any attempt to define comparative levels of efficacy or toxicity.

INCREASED DOSAGE

The significance of the dose-response relationship in germ cell malignancy is controversial. Although there has been an implicit belief that "more is better" for many years, the evidence to support this is not well defined. The Southwest Oncology Group has shown, in a randomised trial, that a dose level of 100 mg/m^2 cisplatin yields a greater response rate and survival than 75 mg/m^2 when used as initial chemotherapy for metastatic testicular cancer [10]. Ozols *et al.* [11] have also supported a dose-response relationship for cisplatin in the treatment of poor prognosis testicular cancer, based upon a randomised trial that compared a standard PVB regimen with high-dose (200 mg/m^2) cisplatin plus vinblastine–bleomycin–etoposide. These regimens yielded respective complete response rates of 67% and 88%, with survival plateaux of 48% and 78%. However, many of the patients in this series would not have qualified as having poor prognosis disease in other centres [5, 7, 8].

Of importance, only a small proportion of patients relapsing

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after PVB maintained complete remissions after second-line treatment with the high-dose schedule [11]. Furthermore, Einhorn has reported a randomised trial of the management of poor prognosis testis cancer that did not show any difference between two schedules of PVB in which the only variable was the dose of cisplatin (100 vs. 200 mg/m^2) [12]. Einhorn proposed that the results of Ozols *et al.* were simply due to the addition of etoposide to the regimen. Furthermore, in a retrospective analysis of 253 patients treated initially with the PVB regimen for good and poor prognosis metastatic disease, the Australasian Germ Cell Trial Group failed to demonstrate any major dose-response effect for vinblastine or bleomycin, although dose intensity of cisplatin was not assessed [13].

It is not clear whether these data can be extrapolated directly to the management of refractory disease. However, others have also failed to demonstrate any sustained benefit from the addition of increased doses of cisplatin (140–200 mg/m^2) to etoposide in the treatment of poor-risk or relapsed germ cell tumours [14, 15].

Wolff *et al.* [16, 17] postulated a dose-response relationship for etoposide, based on phase I and II trials of high-dose therapy with autologous bone marrow transplantation, in which responses (mostly of short duration) were documented in germ cell tumours that had relapsed after prior treatment with conventional doses of etoposide. These data have led to further investigations, as reviewed below.

INCREASED FREQUENCY OF DOSAGE AND NON-CROSSRESISTANT REGIMENS

Several groups have used schedules requiring more frequent delivery of chemotherapy than the usual 21-day cycle, and/or drugs that are likely to offer different spectra or mechanisms of activity from the initial regimens that were used (non-crossresistance). Arising from the highly successful treatment of high-risk, metastatic gestational choriocarcinoma, Newlands and colleagues at Charing Cross Hospital, London, developed the POMBACE regimen for high-risk germ cell tumours [18]. This approach involves the use of cycles of cisplatin–vincristine–methotrexate–bleomycin alternating with actinomycin–cyclophosphamide–etoposide, administered at 10-day intervals, irrespective of blood count. This has yielded sustained responses in more than 70% of patients with poor-risk germinal malignancy [18, 19]. While our own experience with this regimen as initial treatment of high-risk disease has produced equivalently high cure rates, only 30% of patients treated in a salvage setting have been cured (D.R. *et al.*, unpublished).

A similar philosophy of treatment or high-risk disease has been explored by the European Organization for the Research and Treatment of Cancer, using a rapid cycling regimen of bleomycin–vincristine–cisplatin, followed by 21 day cycles of etoposide–ifosfamide–cisplatin (BOP-VIP) [20] with similar results. Wettlaufer *et al.* have also achieved high complete response rates and sustained remissions in patients with poor risk disease using weekly doses of vincristine, bleomycin and cisplatin [21].

Although not addressing the frequency of drug delivery, the Australasian Germ Cell Trial Group recently reported 29% of 51 patients who achieved complete remission or who underwent complete resection of residual masses (CR + NED) in response to a salvage regimen incorporating etoposide, actinomycin and methotrexate, without the use of cisplatin [22]. In this series, patients had initially been treated with cisplatin, vinblastine and bleomycin [9], and thus the salvage regimen reflected an attempt to effect complete non-crossresistance. All patients in the CR + NED group remained free of disease beyond 5 years [22].

Others have combined a broad spectrum of drugs, delivered at conventional 21–28 day intervals, to provide initial non-crossresistant therapy for high risk tumours [23, 24]. However, a broad range of outcomes have been achieved, with reported cure rates in the range of 20–90%, and the true utility of this approach remains unclear. In addition, the role of these regimens against relapsed cancer has not been defined.

NEW DRUGS

Because of the paucity of patients with previously treated germ cell tumours, and the large number of established agents known to be active in this context, the introduction of new agents into the managment of relapsed germinal neoplasia has been slow. Several agents have been assessed without having a major impact on current practice, including vindesine [25, 26], amsacrine [27] and 13-cis retinoic acid [28]. However, it should be noted that vindesine had demonstrable antitumour activity, with a 15% response rate in previously treated patients [26].

Nevertheless, three important new drugs have been introduced into salvage treatment. Fitzharris *et al.* [29] showed that etoposide is active against testicular cancers that had relapsed after PVB, yielding an overall response rate of 45%, an observation confirmed in several other reports [30]. Williams *et al.* [31] reported similar response rates when cisplatin (100 mg/m^2) was combined with etoposide as salvage therapy, although the respective series of treated patients were not comparable. Similarly, the combination of etoposide, doxorubicin and cisplatin is active in this context [32].

Clinical trials effected in Europe first demonstrated substantial activity of ifosfamide against relapsed germ cell tumours, with response rates of up to 30%, depending upon the dosage employed and criteria for entry onto protocols [33]. The dose-limiting toxic effect of haemorrhagic cystitis was overcome through the use of the sulphydryl uro-protective agent, mesna, allowing the high doses of current practice (4–12 g per course) to be employed with safety [33, 34]. Despite clear evidence of antitumour activity, most responses were only of short duration. Susequently, ifosfamide has been combined with etoposide for the treatment of refractory germ cell tumours, yielding a response rate of 42% [35], and with etoposide and cisplatin to produce a response rate of 70% and 15% survival beyond 12 months [36].

Carboplatin, a second-generation platinum coordination complex with a lesser profile of toxicity than cisplatin, has been shown to be active as a single agent against relapsed germ cell tumours, although achieving only transient remissions when used in conventional dosage [37]. To our knowledge, the application of conventional doses of carboplatin (300–500 mg/m^2) in combination regimens for resistant germ cell tumours has not been reported. However, as discussed below, Nichols *et al.* [38] have shown substantial antitumour activity of a high-dose carboplatin-containing regimen with autologous marrow support.

AUTOLOGOUS BONE MARROW TRANSPLANTATION

The use of high-dose chemotherapy followed by autologous bone marrow transplantation (ABMT) has offered a potentially attractive option for consolidating the effects of standard dose salvage chemotherapy when there is a high level risk of relapse. The patient population is young, dose-response relationships have been postulated for some of the drugs that are active against

germ cell tumours, and germ cell tumours usually do not spread to the bone marrow. Furthermore, it has been suggested that ABMT has been useful in the primary treatment of germ cell tumours with poor prognostic factors [39–41].

Although many investigators are currently evaluating the role of ABMT in the salvage setting, its true merit remains difficult to determine because of the heterogeneity of the patient population and the small numbers available for randomised assessment, as outlined above. In addition, there has been no standard preparatory regimen; etoposide, melphalan, cyclophosphamide, ifosfamide, cisplatin, carboplatin, bleomycin and carmustine have been used in various doses and combinations, although the more recent studies have most often employed cisplatin, ifosfamide and etoposide. Moreover, the preparatory regimen has been employed as part of two successive transplant attempts in only few studies, and thus it is not yet clear whether these techniques will be applicable to protocols that require repetitive dosing.

Despite these limitations, some trends have emerged. The pattern of toxicity has been severe, with more than 50% of patients experiencing grade 4 toxicity and prolonged periods of hospitalisation, and up to 25% of patients dying from the side-effects of treatment. The predominant patterns of toxicity have been predictable, including severe myelosuppression, mucosal, gastrointestinal, renal and neurological damage, although a detailed assessment is beyond the scope of this overview. However, in any analysis of the role of this approach, the severe patterns of toxicity must be weighed aginst the efficacy of treatment of a potentially lethal illness.

Response rates of 30–50% have frequently been reported after treatment of relapsed/resistant germ cell tumours with these regimens, although often of only short duration. However, relapsed tumours with a sustained response to chemotherapy before ABMT ("drug sensitive" relapse) have maintained a high proportion of continuing responses after ABMT. Biron *et al.* [40] reported that 6 of 8 patients in drug sensitive relapse were free of disease following treatment with cisplatin, etoposide and ifosfamide at 3+ to 21+ months. Similarly Ahlgren *et al.* [42] noted that each of 3 complete responses persisted from 10–34 months, and Baume *et al.* [41] reported 4 of 5 patients remaining in complete remission at 42–48 months. Of course, this represents a highly selected group, and illustrates the potential pitfalls of interpretation through bias in selection or reporting.

Moreover, the specific role of ABMT, in addition to the impact of the preceding chemotherapy regimen, has not yet been defined. Of interest, Droz *et al.* have initiated a randomised trial to resolve this specific issue [39].

In a detailed study, Nichols and colleagues reported a response rate of 44% among 32 patients with relapsed/resistant tumours treated in a phase I–II trial of dose escalation of carboplatin in combination with high-dose etoposide [38]. No attempt was made to achieve tumour cytoreduction before high-dose therapy. 4 patients remain in continuous remission (3 longer than 1 year), although 21% died from treatment. Of importance, this report did not specify whether there was any difference in outcome between tumours that had relapsed and those that were primarily resistant to chemotherapy.

Patients with progressive tumours during the course of front-line or salvage treatment often do not appear to benefit from ABMT. For example, Baume [41] reported only 3 complete responses among 12 patients refractory to cisplatin-containing regimens; all patients had died, with a median survival of only 7 months. Similarly, Wolff *et al.* [17] reported that only 2 of 10 patients with persistent or progressive tumours achieved complete remission, each of short duration. Coppin *et al.* [43] found no responses among 4 patients who were refractory to a high-dose salvage regimen that incorporated cisplatin, ifosfamide and etoposide. Similar results have been reported by others [44, 45]. It should, however, be noted that the proponents of ABMT could reasonably claim that the conditioning and treatment regimens in these cases were not yet optimal.

In many published studies, it has not been stated whether patients were responding or refractory to treatment before ABMT. Not surprisingly, these studies have demonstrated outcomes intermediate between the two groups above. Pico *et al.* [46] reported 5 of 16 patients with sustained complete response from 7+ to 13+ months after ABMT. By contrast, Biron *et al.* [47] reported only 2 unsustained complete remissions among 15 patients with relapsed or persistent disease. Blijham *et al.* reported a median duration of response of only 16 weeks for the 4 heavily pretreated patients who achieved CR among a series of 13 cases [48]. Similarly Mulder *et al.* [45] treated 5 patients with relapsed tumours that had previously been in complete remission, but was only able to reinduce complete remission (59 weeks duration) in one case.

Although ABMT may have an adjunctive role for the treatment of relapsed tumours that are responding to salvage chemotherapy, its role in other situations remains unclear and will require further study.

FUTURE TRENDS

Two important options for the treatment of refractory germ cell tumours have not been assessed: protection of normal tissues against the toxicity of treatment, and the biochemical or immunological modulation of cytotoxic chemotherapy. As noted above, the use of mesna, a sulphydryl protector against urothelial damage, has facilitated the safe use of higher doses of ifosfamide [33]. However, a preliminary attempt to use intravenous hyperalimentation to protect against gastrointestinal toxicity and weight loss from intensive chemotherapy schedules for testicular cancer failed to yield any useful outcome [49], and may have dissuaded other investigators from pursuing this approach. By contrast, the highly effective function of ondansetron against the emetic effects of cisplatin [50] may facilitate new applications and schedules of administration of cisplatin and other toxic drugs in the treatment of refractory germ cell tumours.

Several clinical trials have demonstrated substantial protection by the colony stimulating factors (CSFs), G-CSF and GM-CSF, (granulocyte CSF and granulocyte–macrophage CSF, respectively) of the bone marrow and of mucosal surfaces against the toxicity of intensive regimens of combination chemotherapy [51, 52] although this application has not yet been reported in the context of refractory testicular cancer. Whether these hormones will ultimately be safe in this young population of patients remains to be proved. It is possible that the CSFs could stimulate tumour growth or could cause late marrow dysfunction or even neoplasia. The latter would be of particular concern in view of the previous documentation of an association between extragonadal germ cell tumours and haematological malignancy [53] and the association between germinal neoplasia and the expression of chromosomal abnormalities and amplification of oncogenes, as reviewed elsewhere [54]. Similarly, the use of high doses of alkylating agents for ABMT could also pose potential late hazards. While the high risk of death from relapsed testicular cancer justifies the use of such innovative approaches

in this patient population, great caution is mandatory in their use.

We do not believe that there is a current state of the art for the management of refractory testicular cancer. We have used dose-intense combination regimens, such as POMBACE [18] and VIP [20] with some success in this context, but with outcomes that are clearly inferior to those achieved for most patients with previously untreated testicular cancer. Because patients with refractory testicular cancer are more likely to die from malignancy than from any other cause, they should be offered participation in some of the newer investigational programmes.

Of particular importance is the need for objectivity in our attempts to overcome this final hurdle in the treatment of testicular cancer. It is essential that carefully defined criteria of refractory disease and stringent assessments of outcome be applied, and that adequate numbers of patients with lengthy follow-up be reported. Ideally, in view of the relative scarcity of such patients, their treatment should be restricted to centres of excellence that participate in innovative, well structured collaborative trials. However, we must also remain vigilant to the hazards of late toxicity, and take care not to apply unproven or excessively toxic regimens to the majority of the patient population with testicular cancer—i.e. those who can expect cure and safety from our current conventional methods.

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Towards Improved Cancer Diagnosis and Treatment Founded on Current Developments in the Basic Sciences: Options for Intensified European Efforts

An EORTC Research Branch Scientific Advisory Board Consensus Paper

RAPID AND EXCITING advances during the past few years in the areas of molecular genetics, cell and developmental biology and immunology have resulted in an increased demand for improved and intensified interaction between basic research and clinical oncology in Europe. In order to accelerate the transfer of information and innovative concepts derived from "new biology" to the clinic, the Research Branch of the EORTC has appointed a Scientific Advisory Board, which consists of basic scientists and several clinical oncologists. The function of the board is to evaluate continuously developments in the basic sciences and their potential for application in clinical oncology. In a process of further re-evaluation within the EORTC Research Branch, recommendations from the Boards are subsequently condensed into Consensus Papers, the first of which is presented here. In addition, this paper describes the activities of several EORTC Research Groups concerned with the development and evaluation of anticancer agents. While primarily intended for European researchers and clinicians, the information contained in these Consensus Papers should also assist European science funding agencies—and the Commission of the European Com-

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