Germ-cell tumor survivors: the price for cure

Treatment integrating chemotherapy, surgery and radiotherapy results in a high cure rate in patients with disseminated germ-cell tumors (GCTs). According to the International Germ Cell Cancer Collaborative Group (IGCCC) classification, a cure can be achieved in 92, 80 and 48% of good, intermediate and poor prognosis non-seminomatous GCT (NSGCT), respectively, and in 86 and 72% of good and intermediate prognosis seminomas, respectively [1]. Studies performed in the 1990s have shown that even higher cure rates can be achieved, although there has been no demonstration of a better treatment than bleomycin, etoposide and cisplatin (BEP) in NSGCT [2–4]. Ideally, the early identification of patients who are not likely to be cured by standard therapy would allow the use of an alternative therapy (albeit with a potentially higher toxicity than BEP) for this very select population of patients. Although we can anticipate that new biological tools such as advances in genomic technology will help to reach this objective (i.e. identification of patients with non-responsive disease), the rarity of these neoplasms makes it unlikely that this can be achieved in the near future. However, recent re-evaluation of an old technique (namely, the observation of the decline rate of tumor markers) suggests that we can currently design trials with an early switch of regimen when the probability of cure is not high [5, 6]. Such trials are currently ongoing or about to begin in Europe and the USA. The main objectives of these clinical trials are to increase the cure rate in patients who have an unsatisfactory decline in tumor markers and to limit toxicity in those with a satisfactory decline.

The issue of toxicity resulting from the treatment is of special concern in a population of young men with an overall probability of cure of at least 70–80%, even in disseminated disease, and >98% in stage I cases. Long-term side effects need to be considered since patients who reach the stage of complete response are likely to live for decades. Previous studies on the reduction of toxicity levels associated with the BEP regimen, by deleting or replacing a drug, have mostly been unsuccessful. However, their results have provided valuable information for clinical practice. The preliminary finding from a randomized trial [7], that four cycles of the cisplatin–etoposide (EP) regimen seems equivalent to three cycles of BEP in good prognosis NSGCT patients, provides a rationale to use this former regimen in patients in whom the risk of lung toxicity is not acceptable (e.g. professional scuba diver, trumpet player). Another well known example of treatment individualization is the impressive story of the cyclist, Lance Armstrong. His physicians in Indianapolis switched him to the etoposide, ifosfamide and cisplatin regimen, in an attempt to prevent lung damage, after a single cycle of BEP for poor prognosis disease. The treatment resulted in complete remission and he went on to win the Tour de France three times (so far!) [8]. Finally, another example was recently provided when a physician, highly experienced in the treatment of GCTs, acknowledged he had been using carboplatin instead of cisplatin to avoid loss of high-tone hearing in very selected cases of professional musicians, although he was aware that carboplatin has proven inferior to cisplatin in randomized trials of good prognosis NSGCTs [9].

In this context, two papers reported in this issue of *Annals of Oncology* are of significant importance. The first paper is published by Strumberg et al., from the University of Essen [10]. The authors performed a detailed retrospective study on long-term toxic effects in 32 survivors of disseminated NSGCT. The relatively small number of patients is counterbalanced by the impressive amount of data available per patient. The problems with this trial were that the patients received a regimen that included doxorubicin (which is not usually used in NSGCTs), the absence of a control population and the fact that only 32 of 55 long-term survivors that were assessed for long-term toxicity eventually participated in the trial. Patients were planned to receive six cycles of two regimens (vinblastine–bleomycin and cisplatin–doxorubicin) given sequentially. The minimum follow-up was >13 years. The main point of the paper is that GCT survivors have an unfavorable cardiovascular risk profile. Indeed, their results show that 30% of the patients had abnormal left ventricle function (although the cumulative dose of doxorubicin in these patients was only 207 mg/m², range 58–280 mg/m²), serum cholesterol was elevated in 82% and diastolic arterial hypertension was detected in 23% of patients. These results confirm previous findings that patients with GCT are at high risk of both venous and arterial cardiovascular events [11–15]. Whether this is due to a direct effect of chemotherapy, a pre-existing condition in patients with GCTs, hormone modifications induced by the treatment or a combination of these factors, is unknown.

The second point of the paper is that even with a long delay after therapy, peripheral neurotoxicity and ototoxicity remain issues since roughly one-third of patients still have symptoms of either one or both toxicities. Moreover, the incidence of ototoxicity remained the same in patients who had received <400 mg/m² of cisplatin. Although various biases may partly explain these results [i.e. the planned number of cycles (n = 6)]
is high by current standards and patients with symptomatic long-term side effects are probably more likely to be in the group of 32 patients who gave their consent to participate in the study while asymptomatic patients are more likely to belong to the 23 who did not, these long-term toxic effect rates in a population of patients with a median age of 40 years should be cautious. Attempts to decrease neurotoxicity were successful in the 1980s when vinblastine was switched to etoposide and when consolidation chemotherapy was deleted from standard treatment [16, 17]. Unfortunately, attempts to replace cisplatin with carboplatin have failed and cisplatin-induced toxicity is still a concern in patients with GCTs. Thus, the clinical development of a neuroprotector is urgently needed. Only a few studies have been published on this topic [18, 19].

The second paper is a report by Fossa et al. [20], which focuses on long-term renal function in GCT survivors. To assess the renal toxicity of chemotherapy and radiotherapy, the authors used a group of patients managed by retroperitoneal lymph node dissection as controls. As expected, the data shows that patients who received cisplatin, especially those who received a high cumulative dose (>850 mg), had a significantly lower value of long-term renal functions compared with controls. Probably more unexpectedly, the results also showed a long-term renal impairment in patients managed with radiotherapy alone compared with controls, although the doses of radiation used (36–40 Gy) would be considered high by current standards. The study further demonstrated that renal impairment occurs immediately after chemotherapy, but is delayed by 3–5 years after radiotherapy. In both cases, no further improvement of renal function is likely to occur. Therefore, these results are a plea for a new appraisal of how better to integrate radiotherapy (and doses of radiotherapy), chemotherapy and surveillance in the early stages of GCTs. Since a link between radiotherapy (at least at doses >30 Gy) and the occurrence of second neoplasms has recently been shown [21], many arguments for reducing therapy in patients with early seminoma can be made.

The use of out-dated regimens and the use of unnecessary (by current standards) consolidation therapy are two of the problems in current reports on long-term toxicity in GCT survivors. With this in mind, the long-term results of the phase III trial comparing three cycles of BEP with four cycles of EP [7] are eagerly awaited. The preliminary results of this trial suggest equivalent efficacy, and long-term assessment of various toxic effects was planned in the study protocol. In stage I seminoma, a randomized trial of radiotherapy versus single-agent single-dose carboplatin has now completed its accrual. Results of this trial on disease control, toxicity and quality of life will also be of major interest in defining a better management standard.

There is obviously a need to better separate the two forms of toxicity, acute and chronic. The acute side effects appear to be greatly modified with standard regimens and recent progresses in their management. However, the long-term toxicities, which have the potential to greatly alter the quality of life in these young individuals, remain a challenge. Such toxicities mainly include compromised renal function, increased risk of cardiovascular disease, neurotoxicity, social disruption and disengagement, and infertility. A major area of specific scientific discovery and improvement of therapy must be towards moderating these specific side effects, so that the goal of curing patients and returning them to their normal state can be attained. In order to achieve this, a classification of toxicities which ranks them in order of importance for disrupting the quality of life needs to be devised. This will provide a foundation for the development of new studies targeting this approach.

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