Miracles don’t happen any more

Germ cell cancers still remain among the most curable adult solid cancers. The majority of patients present with early stage disease that is limited to the testis. Active surveillance after orchectomy emerges as a new treatment option avoiding any form of chemotherapy for a substantial proportion of these patients while maintaining a cure rate of close to 100%. Even patients with metastatic, but limited ‘good risk’ disease according to the IGCCCG classification enjoy a high likelihood of cure, if adequately treated.

What a contrast to those unfortunate patients, who relapse after three or four cycles of curative intent first-line chemotherapy, or who even become refractory to such treatment. The probability of cure after failure of cisplatin-based first-line chemotherapy drops to ~50% overall even with modern salvage strategies. While this might be dazzling in other tumors, such a perspective is entirely unacceptable in germ cell cancer. In this issue of Annals of Oncology, Selle et al. [1] try to push beyond this limit by modifying their already successful previous salvage strategy (TAXIF I) in a follow-up phase II study (TAXIF II) in 45 patients with seminomas and non-seminomas.

The TAXIF II regimen combines an initial phase of alternating non-platinum-based chemotherapy with etoposide, carboplatin, and thiotepa with two cycles of high-dose carboplatin, etoposide and ifosfamide. Only patients with a relapse or progression after at least one (non-seminomas) or two lines (seminomas) of cisplatin-based chemotherapy and cisplatin-sensitive, histologically proven active cancer could be included. Therefore, the target salvage population was clearly met. As expected in a phase II trial, the primary end point of the study was the rate of complete responses after chemotherapy, which was 16% overall. The overall rate of favorable responses that also included patients with tumor marker-negative partial remissions was 42%, and 44% of patients with residual disease and either negative or positive tumor markers could be taken to residual tumor resection. These results are not superior compared with other salvage series that have reported even higher response rates using sequential high-dose chemotherapy with carboplatin and etoposide alone [2–4]. The main secondary end points, and the most relevant ones in respect to patient benefit, were progression-free and overall survival. Although the trial stopped recruiting in 2007, the median follow-up of 26 months was short, indicating that almost half of the patients had not passed the critical landmark of 2 years. Therefore, the progression-free survival probability of 50% and the overall survival probability of 66% in this series must be interpreted with caution and expected to drop with more mature observation.

The TAXIF II regimen is clearly active and able to induce clinically relevant responses and long-term remissions even in patients failing previous cisplatin-based conventional-dose treatments, as evidenced by the data presented in this issue. However, the TAXIF II regimen is also surprising as according to this protocol patients with cisplatin-sensitive relapses do not receive a platinum compound for at least 8 weeks. Even more surprising, patients progressing during this period of non-cisplatin-based treatment are considered non-responders and taken off protocol. As expected from an intensive salvage regimen, the TAXIF II protocol is toxic with a substantial number of grade III and IV toxicities including a substantial proportion of neurotoxicity that seems to be higher compared with other salvage regimens. As a result only about two-thirds of patients could receive their scheduled treatment. The remaining patients had to be taken off protocol mainly due to toxic side-effects, co-morbidities, or refusal to continue treatment [1].

Selle et al. have to be congratulated on completing a study in a difficult clinical scenario, demonstrating that even patients with multiple relapses can successfully be salvaged if expertly treated. However, does the trial address the main issues in the management of relapsed or refractory germ cell cancer, or are the results likely to change the current management of such patients? My answer to both questions is unfortunately no.

Miracle don’t happen any more. In retrospective series, sequential high-dose chemotherapy seems to improve survival probabilities and cure by ~10% compared with conventional-dose salvage treatment [5]. It is unlikely that beyond this improvement, modifications of the existing backbone of sequential high-dose carboplatin and etoposide will have a major impact on long-term overall survival or cure. Choose an existing high-dose strategy with proven efficacy, apply this expertly, control concomitant toxicities and orchestrate the sequence of timely and intensive chemotherapy well with expert residual tumor resections, and the results will most likely compare to the successes of published series.

Patients with relapsed and refractory germ cell cancer are a highly heterogeneous patient population. During the past two decades, numerous phase II trials similar to the one presented by Selle et al. have demonstrated that the impact of prognostic factors such as histology and tumor biology, the intensity and duration of previous treatments and the responses hereupon as well as the disease location and overall disease burden at the time of salvage treatment impact more on response and survival probabilities than any particular salvage strategy chosen [6]. The main differences between existing high-dose strategies lie in their toxicity profiles. To this end, the TAXIF II protocol with its peculiarities and its rate of grade III and IV toxicities is unlikely to change the current standard in cisplatin-sensitive patients of mobilizing chemotherapy followed by two or three upfront cycles of high-dose carboplatin and etoposide.

If it is not TAXIF II or yet another blend of agents, what are the main issues relevant in the management of relapsed and refractory germ cell cancer?

Although it may sound odd, number 1 is expert first-line treatment. Many relapses can be avoided. More often than not colleagues at referral centers still see patients whose first-line treatments had been simply messed up. Why do we still accept in many European countries that patients with germ cell cancer are being treated across institutions with whatever ingenious, but unproven strategy is at hand? The data are out: survival is...
better, toxicity is less if these patients are treated at expert centers! It is more than overdue that germ cell cancer treatment should only be delivered at centers with sufficient case load and expertise. And this is, most likely, not the practice or hospital next door, sometimes not even if it is a tertiary university center. Dedicated teams and expertise improved results in other cancer types, they will do the same in germ cell cancer too.

Number 2 is that all arguments listed above apply even more for salvage treatment. While less experienced physicians might still be able to manage three to four cycles of first-line chemotherapy, most of them get hopelessly lost, if this treatment fails. Salvage or savage treatment: an editorial some years ago in *Annals of Oncology* says it all [7]. We have not got any better since then. And here lies the real strength of TAXIF II and similar phase II studies: they centralize treatment at referral centers and within the structure of a protocol.

Number 3 means phase III. There is still the ongoing debate about the superiority of high-dose over conventional-dose first-salvage treatment. Unless we perform the cooperative effort of a randomized phase III trial comparing modern type conventional-dose treatment with the best available high-dose strategy, we will continue to argue about this in years to come. The lack of funding and bureaucratic hurdles have hampered such a trial in recent years, but a trial by the acronym of TIGER will hopefully be activated and led by investigators in the USA and Europe. The good news is that organizations like ‘Movember’, ‘Orchid’, and the ‘EORTC’ have realized the need and tuned in. A large multicenter phase III trial like TIGER will also help to address issue number 4: to collect data on the biology of relapsed and refractory germ cell cancer in order to learn more about why these cancers have become so nasty.

Miracles don’t happen any more and are unlikely to happen with yet another blend or mixture of existing agents—but we would save many additional lives, if we applied proven strategies expertly and focussed our efforts in a structured way. Do centralize germ cell cancer treatment! And yes, of course, do participate in the TIGER trial once it is open to accrue.

Jörg Beyer
Department of Oncology, University Hospital Zurich, Zurich, Switzerland
(E-mail: joerg.beyer@usz.ch)

disclosure
The author has declared no conflicts of interest.

references