**Patients with advanced non-seminomatous germ-cell tumour: the art of the start**

Even at advanced stages, germ-cell tumours are a highly curable disease with cure rates as high as 80% [1]. This outcome is unsurpassed in any other solid tumour and has been made possible by intensive and highly effective cisplatin-based combination chemotherapy. However, treatment can come at a price. Even though the vast majority of patients with non-seminomatous germ-cell tumours are otherwise healthy individuals, and the median age at diagnosis is 25–30 years, treatment can be lethal in a significant proportion of patients with metastatic disease. In trials, treatment-related mortality has been reported in the range of 2%–7%, irrespective of the use of first-line high-dose chemotherapy or conventional treatment [2–5]. Since patients with a seriously impaired general status of health due to either tumour burden or other medical conditions are often excluded from clinical trials, the treatment-associated rate of deaths could be even higher, especially in patients presenting with an impaired general status of health. Risk factors predictive of complications occurring early during the course of the treatment are poorly defined. Reports of two small patient series identified poor performance status (PS) as a significant pre-treatment factor for severe toxicity after cisplatin-based chemotherapy [6, 7]. As germ-cell tumours are among the fastest growing solid tumours [8] and show an exquisite response to chemotherapy, it is not surprising that case reports have described the phenomenon of tumour lysis syndrome in patients with metastatic tumours and highly elevated tumour markers, sometimes showing a fatal outcome [9, 10]. Other authors, however, have questioned the existence of tumour lysis syndrome in germ-cell tumour patients [11, 12]. Less questionable seems the existence of a different condition with high lethality termed ‘choriocarcinoma syndrome’ or ‘very high risk germ-cell-tumours’, which is characterised by the development of an acute respiratory distress syndrome (ARDS) shortly after the induction of chemotherapy in patients with extensive thoracic tumour burden (either lung metastases or mediastinal bulk) and mostly elevated human chorionic gonadotropin (hCG) [13–15]. Massive cell death due to chemotherapy and consequent release of cytokines, potentially aggravated by tumoral and/or alveolar haemorrhage, has been postulated as the mechanism underlying this syndrome [16]. Especially in patients with ARDS after chemotherapy requiring mechanical ventilation, the outcome was very poor. Therefore, the stakes are high when treatment is initiated in a patient presenting with an advanced non-seminoma and extensive tumour burden, signs of imminent respiratory failure, and/or poor PS. The clinical management under these circumstances is not well defined, and clinical guidelines like the European Germ Cell Cancer Consensus [17] offer no information on how to approach the treatment of critically ill patients.

In this issue of the *Annals of Oncology*, two groups, one from London and one from Paris, publish their approach to initiation of chemotherapy treatment in those patients with poor prognosis non-seminomatous germ-cell tumours where treatment-related complications are anticipated. For the English group, Gillesen et al. [18] report a case series of 20 patients where induction chemotherapy with ‘baby-BOP’ (bleomycin, vincristine, and cisplatin) (bBOP) was administered before standard chemotherapy. The patients presented with a poor PS or other conditions impairing their health status. The outcome of this approach was compared with a control group from the same centre that was managed without low-dose induction chemotherapy, Massard et al. [19] from the French group report on 25 patients with extensive pulmonary metastases, dyspnoea, or hypoxia at presentation, and elevated hCG levels. Ten of those 25 patients received a 3-day induction chemotherapy with etoposide and cisplatin (EP) rather than a full course of therapy in the first cycle. In addition, bleomycin was postponed to day 15 or omitted during first cycle, and the use of granulocyte colony-stimulating factor (G-CSF) was considered on a case-by-case basis to avoid neutropenia.

Although seemingly tackling the problem of optimal management at initiation of therapy in high-risk patients in the same way, i.e. by the use of less than standard dose induction chemotherapy, and both groups stress the importance of avoiding treatment delay in the subsequent course of treatment, there are considerable differences in the treatment approaches and the underlying philosophy presented by the two groups. The intention of the English group was to ‘safely obtain disease control, alleviate tumour-related symptoms, particularly in those situations where standard therapy may cause complications resulting in difficulties giving subsequent cycles’, and their choice of drugs particularly aims at avoiding myelosuppression. Their use of induction chemotherapy is in line with clinical practice in rapidly proliferating neoplasms, such as leukaemias or lymphomas, when highly effective treatment meets extensive tumour burden and starting low can avoid tumour lysis and general deterioration. The French group, on the other hand, was trying to specifically avoid pulmonary complications by lowering front-line chemotherapy doses, omitting bleomycin in the first 2 weeks of therapy, and ameliorating neutropenia by application of G-CSF when clinically indicated. In contrast to the first report, their approach is tailored to a clearly defined group of patients at high risk of ARDS, where further pulmonary stress, be it by necrosing tumour cells or cytotoxic drugs, is to be avoided.

In the case series of Gillesen, use of bBOP, which consisted of cisplatin 50 mg/m², vincristine 2 mg, and bleomycin 30 mg on day 1, resulted in little haematologic toxicity apart from an increased incidence of anaemia during the first cycle of standard chemotherapy. No toxic deaths or cases of...
neutropenic fever were observed in these patients characterised by a heterogeneous profile of one or more of the following: poor PS, inferior vena cava obstruction, hydronephrosis or renal impairment, imminent or present respiratory failure, or severe bleeding. The overall survival rate was identical between the case and the control series (79% versus 80%). The group concludes that treatment with bBOP is well tolerated, does not seem to adversely affect subsequent treatment, and can therefore be given safely to patients in critical circumstances. However, the authors admit that there are certain shortcomings of their work. One is the retrospective nature and another the small number of patients evaluated. In our view, however, the most critical point is that due to the heterogeneous group of patients treated in this series, it is hard to deduce a clear indication in which situation bBOP should be preferred to standard treatment. Unfortunately, the group does not report whether bBOP resulted in improvement of the PS in those patients that started with a PS of three or more. From the laboratory values reported, neither creatinine nor urea decreased upon administration of induction chemotherapy, but there was a marked decline in tumour markers. It most also be kept in mind that the choice and dosage of the drugs used in bBOP in critically ill patients are not without dangers: both 50 mg/m² cisplatin and 30 mg bleomycin can be disadvantageous when severe renal impairment is present, and administering additional bleomycin to the usual dose given within four cycles when PEB (cisplatin, etoposide, and bleomycin) chemotherapy brings the total dose dangerously close to the absolute limit of 400 mg. In fact, already a cumulative dose of >300 mg bleomycin has been identified as an independent risk factor for pulmonary toxicity [18]. Finally, the activity of vincristine, that can augment polyneuropathy induced by cisplatin, is not very well defined in germ-cell tumours. These considerations offset in our opinion the advantage of the limited haematologic toxicity associated with the use of bBOP. In conclusion, the report suggests that the use of bBOP does not seem to be harmful to patients with advanced disease in a critical state of health. Whether it is truly beneficial, on the other hand, is hard to say.

In the report by Massard et al., treatment details of 10 patients treated from 1997 to 2006 (cohort 2) presenting with pulmonary metastases and dyspnoea or hypoxia are retrospectively compared with data from 15 patients with a similar presentation, treated from 1980 to 1997 (cohort 1). After having observed a frustrating death rate of 66% (10/15) from 1980 to 1997 in patients with imminent respiratory failure, the group modified the approach to these patients and introduced a 3-day induction chemotherapy with etoposide 100 mg/m² and cisplatin 20 mg/m² (EP). After monitoring and evaluation of the situation, treatment was continued around days 10–15 with the first dose of bleomycin 30 mg (in 6 of 10 patients, the drug was completely omitted during the first cycle) and the remaining 2 days of EP. Standard chemotherapy with the first cycle of classical PEB was initiated at day 21. Importantly, all patients were treated in a specialised intensive care unit of this national tertiary centre. This approach resulted in a statistically significant reduction in both the incidence of ARDS (cohort 1: 87% versus cohort 2: 30%) and the mortality due to ARDS (66% versus 20%). Long-term survival in these very high-risk patients was 27% in cohort 1 and 40% in cohort 2. The authors conclude that their strategy of splitting the doses of EP during the first course and avoiding the early use of bleomycin in the course of treatment can help to reduce both ARDS and ARDS-related mortality without compromising long-term outcome. However, they admit that the improvement that they observed after the introduction of this approach could be multifactorial, e.g. influenced by the use of G-CSF and generally improved supportive care in an experienced centre. In our view, the data they present are interesting and can help to guide the management of critically ill patients that are at risk of respiratory failure. The biggest limitation of this series is certainly the small number of only 10 patients, of which even less did eventually receive the chemotherapy regimen the group proposes in the paper, as there was high interindividual variability in terms of treatment the patients actually received during the induction phase. This clearly weakens the recommendations that can be drawn.

All in all, the two papers highlight a rare but clinically very relevant situation: the management of young patients with a potentially curable disease presenting in a state of health that renders them highly susceptible to deterioration and death if standard treatment is applied. As there will never be randomised trials elucidating the optimal management under such circumstances, this level of evidence is the best we will get. At least, the approaches presented here will sensitise physicians involved in the care of such individuals to think about their management and help them to chose appropriate treatment, which will need to be tailored to the situation and the course of the disease. In our view, there are two firm lessons to be learnt from these reports: first, a first cycle of low-dose introduction chemotherapy is a safe and acceptable way to avoid risks associated with standard treatment in certain situations, especially in patients with the so-called ‘choriocarcinoma syndrome’, and second, the management of these patients requires a highly specialised and skilled team including an experienced intensive care unit. This stresses the recommendation of the European Germ cell Cancer Consensus group that for optimal outcome, these patients ‘should be transferred to a specialised centre without any delay’ [17].

F. Honecker & C. Bokemeyer*
Department of Oncology, Haematology, BMT with Section Pneumology, Hubertus Wald Tumorzentrum, University Cancer Center Hamburg, University Medical Center Eppendorf, Hamburg, Germany
(*E-mail: c.bokemeyer@uke.uni-hamburg.de)

References


