The management of non-seminomatous germ-cell tumours patients with viable malignancy at the time of RPLND

What should I do if my first-line chemotherapy has not irradiated all active germ-cell tumour (GCT)? This is the clinical conundrum addressed by Fizazi et al. [1] in this issue of Annals of Oncology, an area of controversy but not a lot of light.

Standard therapy for patients with metastatic non-seminomatous germ-cell tumours remains the use of combination cisplatin-based chemotherapy with the current standard of care being three or four cycles of bleomycin, etoposide and cisplatin (BEP) chemotherapy depending on the prognostic category [2–4]. The majority of patients are cured by such therapy with long-term survival expected in >90% [3–5] except for the minority with poor prognosis disease. Approximately, a third of these patients, however, will be left with residual masses over 1–2 cm for which surgery is advised [most commonly retroperitoneal lymph node dissection (RPLND)]. This advice is given because, though some of these masses (25%–50%) contain necrotic tissue only, the remainder contains either differentiated teratoma (TD) (25%–60%) or undifferentiated tumour (6%–30%) (the relative proportions reflecting differences in case mix and treatment policies) [6–8]. Failure to resect can have substantial impact on patient outcome. For instance in one study of patients treated in the 1980s who had unresected residual masses, 35 of 101 progressed at that site and subsequently 23 died from progressive disease [9]. While residual TD may be responsible for the phenomenon of late relapse which is increasingly reported [10]. Unfortunately, no pre-surgery algorithm have proven effective at predicting histological outcome [6, 11] so surgery has been advised for all patients with residual masses, with some authors advocating resection even for patients with minimal disease [12].

Following surgery, both incomplete excision and the presence of viable undifferentiated GCT carry an adverse prognosis [6, 13, 14]. Patients with viable cancer can obtain a complete remission after surgery and may be cured but relapse is common. How to manage such patients has been the subject of much debate. Following Einhorn’s early work, many authors advocated the use of further adjuvant chemotherapy and this approach has been used extensively to try to improve outcomes. In the relapsed setting, most patients retain a degree of chemosensitivity and thus this further adjuvant chemotherapy has been justified to try to achieve cure while tumour volume remains low. On the other hand, this approach can be criticised as the effectiveness of this chemotherapy in patients who are likely to be at least partially resistant cannot be monitored, adds further toxicity in already heavily treated patients and has not been shown to be clearly improve survival [15].

Uncertainty on this issue has been fuelled by the relatively few patients seen with this problem, even in high volume centres so that few studies report on >30 patients. In the absence of randomised data, which is unlikely to become available, the most robust data is likely to come from the results of two multicentre collaborative studies reported by Fizazi et al. initially in 2001 and now in this current report. The first study reported data contributed from three European collaborative groups (French, Spanish and UK groups) and 12 other European and USA institutions, totalling 238 patients. This study showed that after surgical resection about two-thirds of patients remain progression free and almost three-fourths survive 5 years. An initial International Germ Cell Consensus Classification (IGCCC) good prognostic presentation, a lower volume of viable malignant cells (<10% of viable cells) and complete removal of the mass predicted for better outcome. Indeed, favourable patients (no adverse risk factors) thus having a small volume of residual cancer completely resected had a 5-year survival of 100% if in originally IGCCC good prognostic or 83% if IGCCC intermediate or poor prognosis categories. Only the group with two or three risk factors (~40% of patients) had a relatively poor outcome with a 50% 5-year survival. In this setting, adjuvant chemotherapy improved progression-free survival but not overall survival, though there was a suggestion that intermediate group (one risk factor) patients might do better. There are important limitations to this study: the patients were drawn from a wide range of centres over an extended time period undoubtedly with a range of chemotherapy schedules and practices. Prognostic allocations and histology depended on local reporting. The reasons why some patients received chemotherapy and others did not may vary on local policies but may also be due to unknown local selection practices. The scope for and impact of forseen and unforeseen biases are considerable. For instance, patients receiving adjuvant chemotherapy could be intrinsically a worse group that is then compensated for by use of further chemotherapy.

Given these uncertainties and potential flaws the results, and particularly the prognostic model, of this first study needs validation. Such a validation set is reported in the current article. This report is again a multicentre collaboration involving 13 major cancer centres. It is limited by being only a quarter of the size of the initial publication but does have the advantage of central verification of prognostic factors. The remarkable feature of this report is a close similarity of the outcomes of the two reports with almost identical progression-free and overall
survival reported. This study also confirms the utility of the prognostic index and again show no clear benefit for the use of adjuvant chemotherapy in improving survival.

So where does this study leave us?

First, it means that we have a simple but robust prognostic factor analysis that we can use to aid our decision making. Whether this makes any practical impact on patient management will remain a matter of debate. One has be aware of the heterogeneity of situation within the groups, a ‘one size fits’ all approach for patients within the less good categories may not be appropriate. For instance, the approach for patients classed as intermediate risk on the basis of incomplete excision may be very different from patients who are intermediate because of their pretreatment prognostic category.

Secondly, complete surgical resection is re-iterated as an important factor in determining patient outcome and as such supports results from single-centre studies [6, 8]. Clearly, the issues regarding this are complex. Some aspect of surgical excision is likely to be dependant on tumour-related factors with more advanced bulky disease being more difficult to remove. But this data equally emphasises the importance of specialist surgery in the management of these patients. Of the prognostic factors in this analysis, this is one area that is under our control to influence. We should be aiming to achieve the best possible surgical management of this patient group and, in my view, this means that post-chemotherapy RPLND should be undertaken by expert surgical teams in defined centres of excellence. It remains unanswered as too how to manage patients who despite this are known to have incompletely resected active GCT. The ‘standard’ approach may be considered to be further chemotherapy. But should further local therapy with perhaps radiotherapy be considered as an alternative? A report of sites of failure would be helpful in such a discussion but is probably unobtainable from such a retrospective study.

Thirdly, taken with the first paper, this study I think further weakens the argument for the routine use of adjuvant chemotherapy. It certainly seems unnecessary for patients with no risk factors for recurrence given their excellent outcome in both studies. Given the lack of benefit overall in these studies it questions whether such treatment should be used routinely in other groups. Given that adding additional treatment may add substantially to the burden of acute and late toxicity and that the majority of patients remain disease free after successful surgery, it would indicate that an expectant policy of close observation and early salvage treatment should be the usual approach. The exception may be the cases where there is a strong suspicion of local persistent disease when, after careful patient counselling, further treatment may be appropriate.

In conclusion, the current paper by Fizazi et al. has provided important guidance in managing this small but important group of patients. Not all questions have been answered and, as is often the case, new questions have been posed. Further improvement in our knowledge is unlikely from further such retrospective studies. If we wish to refine treatments further, the tests treatment community will need to come together and design international collaborative prospective studies.

references