Testis cancer: on gilding the lily

One of the wonderful aspects of being an oncologist in the latter part of his career is to be able to reflect upon some successes in this field over the past 30 years. When I was an oncology fellow in the late 1970s, training with Martin Tattersall, Sir Michael Peckham, the late Tim McElwain and the late B.J. Kennedy, I saw first-hand the evolution of management of germ cell malignancy. In my first year as an oncology fellow, I participated, with great sadness and frustration, in the management of many young men with metastatic testicular cancer, treated them with variants of vinblastine–bleomycin or vinblastine–actinomycin–methotrexate, and watched most of them die, much too early.

With one amazing development, the introduction of cisplatin (Bristol Myers Squibb) into standard chemotherapy for testis cancer, developed initially by Einhorn [1], there was a complete transformation from the expectation of early death to the potential of long-term survival in most young men with this dreadful disease [1, 2].

In parallel, we came to understand the significance of the tumor markers elaborated by germ cell tumors. Teams at the University of Minnesota [3], Royal Marsden Hospital [2, 4] and the Danish Testicular Cancer Study Group [5] identified the importance of alpha fetoproteins, the beta subunit of human chorionic gonadotrophin, lactate dehydrogenase isoenzymes and even carcinoembryonic antigen (occasionally) as guides to the presence of germ cell malignancy and its likely histological type. Our early prognostic studies in patients following orchiectomy identified prolonged tumor marker clearance times as seminal in prognostication of worse outcomes [4, 6], and we also demonstrated the importance of T stage and other variables [6, 7]. Prolonged marker clearance was also shown to connote adverse prognosis in patients with metastatic disease [8].

The work building to the identification of prognostic presenting criteria for metastatic disease in the 1980s [9, 10] was also important, culminating in the Consensus Panel Recommendations that divided metastatic germ cell tumors into classifications of good, intermediate and poor prognosis [11]. This allowed the practicing oncologist to give evidence-based information to prospective patients, outlining the chances of success and failure, and identifying the reasons for a detailed and structured plan of action. In general terms, this has worked pretty well, particularly for patients with good-risk disease, who can expect a very high chance of cure. Over the years, we have learned not to tinker too much with the model, discovering that attempts to replace cisplatin with carboplatin (Bristol Myers Squibb) or to delete bleomycin from standard schedules have not yielded the hypothesized benefits [12, 13]. Similarly, dropping the dose has been shown to be harmful, despite the best of intentions [14].

Intermediate-risk cases have been a bit more problematical, and my own sense is that a study that showed three and four cycles of (cis)platinum, etoposide and bleomycin to be equivalent was insufficiently powered with intermediate-risk cases to be completely accurate [15]. The real problem has remained in poor-risk disease, and we still have not worked out a great strategy [16], despite earnest attempts using multiagent chemotherapy [17] and transplant-intense strategies [18].

The key is to encourage patients to present earlier, with clear evidence showing that the delay in presentation is harmful [19]. What a missed opportunity when the hapless US Preventive Services Task Force missed a great opportunity to educate doctors and patients about the benefits of early diagnosis, when issuing their recent ‘yes, we have no bananas’ encyclical [20] which took three pages to remind us that they had no basis for changing their (non)-recommendation on testis cancer screening.

For those without the benefits of early presentation, in my tertiary referral practice, I remain concerned that the most common cause of death in good/intermediate-risk testicular cancer may remain bad clinical decision process, with suboptimal selection of treatment regimens by inexperienced clinicians. For patients with bad-risk disease, referral to centers of excellence which are investigating the novel treatment approaches, in a structured fashion, makes the most sense to me.

So what is the impact of the article from Dr. Massard et al. [21]? It adds to our armamentarium, providing another algorithm for helping us to define prognosis of our patients, and perhaps allowing us to identify patients who will not get a satisfactory outcome at an earlier stage. For many years, we have been aware that acute tumor marker release, particularly for beta-human chorionic gonadotropin, can confuse the interpretation of marker decline profiles—release of this marker can make marker decline curves appear artificially prolonged, suggesting the possibility of innate drug resistance, when in reality the decline reflects a beneficial pattern of response. This problem can be overcome by regular tumor marker sampling, multiple times per week, during the induction phase. If there is a weakness in the present study, it is the potential to misidentify tumor marker release as indicative of failure of therapy. This paper is interesting and provocative, but will require external validation before this approach becomes state of the art. However, poor-risk
testicular cancer is a complex and demanding disease, and it does not seem likely that linear algorithms that attempt to over-simplify the assessment of disease and the selection of treatment regimens will improve our results.

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references

Speeding dating for docetaxel and recent debutsantes in castration-resistant prostate cancer: ‘plus or minus’ may be a minus

Docetaxel confers a survival advantage in men with metastatic castrate-resistant prostate cancer (mCRPC) and can improve the quality of life by palliating cancer-related symptoms [1, 2]. However, only about half of men will experience objective responses and one-third will benefit from pain palliation, leaving room for improvement. Adding something novel to docetaxel in a ‘plus or minus’ clinical trial design has become extremely popular, typically with a targeted or otherwise novel therapeutic agent. Targeted therapeutics are generally developed using preclinical models to identify key malignant signaling pathways on which cancer cells are dependent. Ideally, they are also designed to modulate specific escape or resistance pathways for the chemotherapy to which they will be added. Integrins are one such potential target. The coincidence of the advent of docetaxel in 2004 as the first agent to improve survival and the development of novel targeted therapies resulted in an unfettered desire to ‘make a match’ with hope of synergistic or additive effect. This proverbial ‘speed dating’ has to this point gone unrewarded.

The original contribution from Heidenreich et al. [3] in this issue of Annals describes a randomized, double-blind, phase II study of intetumumab, a monoclonal antibody directed at αvβ3, αvβ5, and αvβ6, in combination with docetaxel compared with docetaxel– placebo in men with mCRPC. Early cessation of the trial was recommended when the interim analysis revealed that not only was there a lack of improvement in the primary end point of progression-free survival (PFS), but there appeared to be a decrement, with median PFS of 7.6

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