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Call for More International Collaboration in Metastatic Seminoma

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In 2006, the largest trial in stage 1 seminoma recruited 1477 patients from 70 hospitals in 14 countries worldwide in 5 yr. The authors reported equivalence between radiation and one course of carboplatin when the dose of area under the curve (AUC) 7 was correctly given; more significantly, they reported a 78% reduction of contralateral testis [1]. If, at the same time, the same centres had recruited their 10–15% of metastatic seminoma cases into a randomised comparison of EP (etoposide and cisplatin) and BEP (bleomycin, etoposide, and cisplatin) and continued it for an additional 5 yr, we would know the relative value of these regimens. Their original persistence as supposedly equal standards of care, despite the 17% worse progression-free survival in a trial in nonseminoma [2], was due to a small randomised study of 146 patients comparing EP with VAB 6 (cyclophosphamide, vinblastine, bleomycin, dactinomycin, and cisplatin) in good-risk nonseminoma, reporting complete response of 93% versus 96%, respectively [3]. The latter regimen has never been tested in a randomised trial against BEP, but cotemporaneous publications showed that it was equivalent to BVP (bleomycin, vinblastine, and cisplatin), which was 6% inferior to BEP [4]. Consequently, this conclusion may not have been valid.

Sadly, a randomised trial of inadequate-dose carboplatin versus EP in 361 metastatic seminoma patients was prematurely abandoned in 1994 [5] because of randomised trial data from nonseminoma [6]. For the last decade, the uncertainty about three courses of BEP and four courses of EP as equivalent standards of care in metastatic seminoma has been perpetuated. This is reflected in the large study over 9 yr reported by Fizazi et al. in this month’s issue of *European Urology* [7]. Despite this criticism, the authors are to be congratulated for prospectively evaluating the prognostic groups of both the old Medical Research Council and the newer International Germ Cell Cancer Collaborative Group, demonstrating their inadequacy, and calling for a prospective evaluation of positron emission tomography (PET)/computed tomography (CT) response in predicting outcome as well as enlarging the database of prospectively collected cases to add to the literature. Despite their apparent good results, a brief review of the literature (by T.O.) continues to suggest that, in terms of continuous progression-free survival, three courses of BEP are at least marginally superior (n = 328, 92% relapse-free survival in seven series with response rates from 88% to 96%) than four courses of EP (n = 313, 88% relapse-free survival in five series with response rates from 82% to 92%). The latter regimen is more expensive for the patient because of 20 d of infusional treatment instead of 9 d. In addition, for many seminoma patients, as shown in the nonseminoma trial of three versus four courses of BEP, it is the fourth 5-d course of cisplatin that causes the most toxicity and delay of full recovery [8].

Although I praise the authors for their tenacity in completing their study, I was disappointed by their pessimism about the possibility of doing any future randomised trials in metastatic seminoma. I accept that patient awareness of testis cancer has increased and that, as Fizazi et al. note [7], there are even fewer metastatic seminoma cases today. However, the spirit of international collaboration that delivered TE19 in 5 yr might require 10 yr to accumulate 400 patients, and that number certainly would not be enough to clarify whether there is a 4% difference between EP and BEP, although it could well determine the relative merits in terms of toxicity. Furthermore, in those centres able to afford PET/CT, we might have randomised data on early PET scan response [9]. If EP was still less effective than BEP, even if not significantly, combination of the randomised cases with the historic nonrandomised data might be enough to convince the
doubters. Equally, increasing evidence shows that escalat-
ing carboplatin dosage to AUC $\times 10$ with 3-yr progression-
free survival of 93% in a series of 61 patients [10] has
produced results as good as those reported for EP. Conse-
quently, one possible solution—given the increasing
patient power in design of studies—would be to engage the
whole international community through an Internet patient
preference registration study with randomisation where
there is equipoise and patient consent such as that
undertaken in prostate cancer, offering BEP, EP, and
carboplatin AUC $\times 10$ for advanced patients and radiation
or radiation plus single-dose carboplatin or carboplatin
AUC $\times 10$ for good-risk 2a and 2b patients.

Such data are not as good as those from a pure
randomised trial, but if data on all cases treated in the
past 10 yr were also collected in a simple database
accessible by modern smartphones, it might just take off.
It would cost relatively little to administer and would mean
that in 10 yr, there will be more information gained than in
the previous 10 yr.

Conflicts of interest: The author has nothing to disclose.

References

[1] Oliver RT, Mason MD, Mead GM, et al. Radiotherapy versus single-
dose carboplatin in adjuvant treatment of stage I seminoma: a

[2] Loehrer Sr PJ, Johnson D, Elson P, Einhorn LH, Trump D. Importance of
bleomycin in favorable-prognosis disseminated germ cell tumors: an
Eastern Cooperative Oncology Group trial. J Clin Oncol 1995;13:
470–6.

cisplatin versus vinblastine + bleomycin + cisplatin + cyclophos-
phamide + dactinomycin in patients with good-prognosis germ cell

Treatment of disseminated germ-cell tumors with cisplatin, bleo-
mycin, and either vinblastine or etoposide. N Engl J Med 1987;316:
1435–40.

Council randomized trial of single agent carboplatin versus etopo-
side and cisplatin for advanced metastatic seminoma. MRC Testi-

etoposide, and cisplatin compared with bleomycin, etoposide, and
carboplatin in good-prognosis metastatic nonseminomatous germ
cell cancer: a multiinstitutional Medical Research Council/European
Organization for Research and Treatment of Cancer trial. J Clin Oncol

etoposide, with or without ifosfamide, in patients with metastatic
seminoma: results of GETUG S99 multicentre prospective study.

[8] Einhorn LH, Foster RS. Bleomycin, etoposide, and cisplatin for three
cycles compared with etoposide and cisplatin for four cycles in
good-risk germ cell tumors: is there a preferred regimen? J Clin
Oncol 2006;24:2597–8, author reply 96–9.

phase 1/2 study of single agent carboplatin in metastatic semi-
noma: potential for acceleration by a new surrogate end point, 72 hr

IGCCCG good prognosis metastatic seminoma. Acta Oncol 2013;52:
987–93.