Eur J Cancer Clin Oncol, Vol. 25, No. 8, pp. 1255–1257, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00
Maxwell Pergamon Macmillan plc

Letter to the Editor

Standardized Objective Criteria of Response—Comments on 'Important Prognostic Value of Standardized Objective Criteria of Response in Stage D2 Prostatic Carcinoma' by Labrie F. *et al.*

D. NEWLING, M.R.G. ROBINSON, L. DENIS and R. SYLVESTER
EORTC GU Group

WE READ with interest the article written by Professor Labrie and his co-workers in the December 1988 issue of *European Journal of Cancer and Clinical Oncology* (Vol. 24, No. 12, pp. 1869–1878).

As members of the EORTC GU Group we feel that we should point out that the EORTC criteria of response quoted by Professor Labrie were those employed in a study which was started some 12 years ago and since that time, as the NPCP criteria have, the EORTC criteria of response have evolved. In the discussion at the end of his paper he compares the NPCP criteria with those of the EORTC and comes to the conclusion that, in many respects, the NPCP criteria are stricter. This is no longer so and the similarities between the two sets of criteria are extremely strong. In particular, the definition of complete response is the same for both the NPCP and the EORTC.

As far as partial response is concerned, the latest EORTC position defines partial response as:

1. No progression of any parameter of disease and no appearance of fresh foci of disease.
2. There should be normalization of bone scan and recalcification of lytic lesions on X-ray.
3. All measurable lesions must decrease by 50% in the sum of the products of their two maximum perpendicular diameters.
4. If the primary lesion is being used as a measurable parameter this too must decrease by 50% of the product of its two maximum diameters, provided one of these diameters measures at least 3 cm.
5. An elevated serum acid phosphatase should return to normal where the elevation was at least two times the previously accepted normal level.

As far as progression is concerned, the EORTC also now accepts that an increase in 25% of the cross-section area of any measurable lesion should be taken as progression. An increase in 50% of the measured cross-section area of the primary may be taken as progression, provided there has been no surgery, radiotherapy or other interference with the primary and provided the patient has not been pretreated with hormone therapy.

We are a little concerned over Professor Labrie's claim that osteoblastic bone lesions can be followed by scintigraphy. Sclerotic bony lesions contain reactive bone formation which is why they calcify. Radionuclcotide bone scans measure the reactive bone in and around a tumour and not the mass of tumour tissue itself. Until a truly reliable method of quantitated isotopic scintigraphy is available it is wrong to claim that bone scintigrams can be used to quantitate the progression or response to treatment of a carcinoma of the prostate.

Professor Labrie also comments on the fact that the EORTC defines a category of no change rather than stable disease. The reason for this is, quite simply, that stabilization of the disease process does not always reflect a response to any treatment which

Accepted 31 March 1989.

is used. Many workers have described stabilization of the disease in patients who are receiving no therapy, either hormonal or cytotoxic, and it is quite clear that carcinoma of the prostate does have this inherent ability to quite inexplicably stop growing [3, 4]. Therefore, for a therapy to be held responsible for stabilization, it must be shown that the disease was progressing before treatment was instituted. In many series, Professor Labrie's included, such a period of progression is not documented. Hence, the only responses which are acceptable in such publications are complete response, partial response or progressive disease.

We must confess to some surprise at the high incidence of complete response quoted in this paper (26.3%). This we find extremely surprising since many workers, Professor Labrie amongst them in the past, have maintained that no prostate cancer is completely hormone dependent and, therefore, it is most unlikely that a complete response is genuine [5, 6]. We find it especially surprising when complete response has apparently occurred in four patients with lung metastases which we know normally carry an extremely poor prognosis. In this context, there are two questions which immediately spring to mind:

1. Was the primary always biopsied after the response had been measured?
2. In those patients who had a complete response and then subsequently relapsed, did the relapse occur at the site of previous metastases or was this evidence of entirely new disease and how did the histology of the recurrent or new occurrence of tumour differ from the primary?
3. Since median times to response are 155, 183 and 401 days respectively for SD, PR and CR, it is not surprising that complete responders have a longer survival. Almost by definition the CR's must survive longer in order to have the necessary time to have a CR.
4. How was the time to stable disease measured in Fig. 1? Since patients were considered as non-responders if there was no stabilization or remission within three months (p. 1871) how is it the average time to stabilization exceeds 90 days in Tables 6 and 7 (median 155 days)?

In the text, Professor Labrie mentions two patients who withdrew from the study because of diarrhoea and we find it rather surprising that this was the only indication of toxicity to Flutamide in a group of patients, some of whom have received the therapy for over 3 years. Certainly, in the Discussion, where mention is made that response is the best predictor of quality of life as well as survival, the presence or absence of toxicity to the therapy must be precisely defined.

The value of any new therapy in an individual tumour can only be assessed when it is tested in a randomized prospective Phase III study against existing therapies. In that context the end points can only logically be survival, time to progression and quality of life and in the Phase III situation, measurement of response is largely irrelevant. The initial results of total androgen blockade, whether with LHRH agonist and Flutamide or orchidectomy and Flutamide or either primary treatment with a different anti-androgen, are at present somewhat equivocal. Two important studies have shown a significant difference, both in survival [7, 8] and time to progression whereas another two have not [9, 10]. If the difference is as small as seems likely between standard therapy and total androgen blockade, and that difference is accompanied by a diminished quality of life, then its value is called into doubt. Only further careful follow up of the prospective randomized series already carried out is going to answer the question and place this treatment in its true context. In that respect, while the conclusions of Professor Labrie's very large Phase II study are of some interest, they do not significantly alter our concept of this treatment in the overall management of patients presenting with metastatic prostate cancer.

REFERENCES

1. Newling DWW. Response criteria in prostate cancer. In: *EORTC GU Group Monograph II, Part A, Therapeutic Principles of Metastatic Prostate Cancer*. New York, Alan R. Liss, 205–220.
2. Newling DWW. Criteria of response to treatment with LHRH agonist in advanced prostatic cancer. In: Motta M, Serio M, eds. *Hormonal Therapy of Prostatic Diseases—Basic and Clinical Aspects*. Medicom, 1987, 206–215.
3. Newling DWW, Hall RR, Richards B, Robinson MRG, Hetherington J. The natural history of prostate cancer—the argument for a no treatment policy. In: Pavone Macaluso M, Smith PH, Bagshawe M, eds. *Testicular Cancer and Other Tumours of the Genito-urinary Tract*. New York, Plenum Press, 1985, 443–449.
4. Handley R, Carr TW, Travis D, Powell PH, Hall RR. Deferred treatment for prostate cancer. *Br J Urol* 1988, **62**, 249–253.
5. Labrie F, Veilleux R. A wide range of sensitivities to androgens developed in cloned Shionogi mouse mammary tumour cells. *The Prostate* 1986, **8**, 293–300.

6. Coffey DS, Isaacs JT. Experimental concepts in the design of new treatment for human prostatic cancer. In: Coffey DS, Isaacs JT, eds. *Prostate Cancer, UICC Technical Report Series.* Geneva, UICC, 1979, Vol. 48, 233–260.
7. Beland L, Elhilali M, Fredet Y *et al.* Total androgen blockade versus orchidectomy in Stage D2 prostate cancer. In: Murphy GP, Saad K, Kous R, Charlan C, Denis L. *Prostate Cancer, Part A, Research Endocrine Treatment and Histopathology.* Progress in Clinical Biological Research, New York, Alan R Liss, 1987, Vol. 24, 243a, 391–400.
8. Crawford ED, McLeod D, Dorr A *et al.* A comparison of Leuprolide with Flutamide and Leuprolide in untreated D2 prostate cancer. INT. 0036. Paper read at the International Symposium on Endocrine Therapy, Monaco, 19–21 November 1988.
9. Iversen P, Hvidt V, Krarup T, Rasmussen F, Rose C, The Danish Prostatic Cancer Group. Zoladex and Flutamide versus orchidectomy in the treatment of patients with advanced carcinoma of the prostate. Abstract No. 43: Paper read at the 8th Congress of the European Association of Urology London, 19 May 1988.
0. Smith PH, Newling DWW, Denis L, Sylvester R, De Pauw M, members of the EORTC GU Group. Orchidectomy versus total androgen blockade—Phase III EORTC GU Group study No. 30853. Abstract No. 42: Paper read at the 8th Congress of the European Association of Urology, London, 19 May 1988.