ELSEVIER

European Journal of Cancer 39 (2003) 2567–2568

European Journal of Cancer

www.ejconline.com

Letter

Reply to comment on "Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders"☆

S. Smeland*, C. Müller, G. Sæter

Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, NO-0310 Oslo, Norway

Received 26 August 2003; accepted 27 August 2003

The interesting letter by Bacci and colleagues published in this issue points out the prognostic impact of serum alkaline phosphatase (sALP) and serum lactate dehydrogenase (sLDH) in a recent analysis from the Rizzoli institute involving 620 osteosarcoma patients. In our recent publication in the *European Journal of Cancer* analysing 113 patients in the study Scandinavian Sarcoma Group Osteosarcoma Study (SSG) VIII, we reported no significant impact of ALP on outcome [1]. Bacci and colleagues suggest that this observation is due to the relatively limited number of patients in our study.

The letter by Bacci has prompted us to re-analyse the SSG VIII data. In the published report [1], sALP was not corrected for gender and age as stated originally. This led to 87% of patients having elevated levels. A re-analysis applying the age and gender adjusted method of Bacci and colleagues [2] reduced this figure to 24% (compared with 46% in Bacci's series). A new multivariate analysis of metastasis-free survival applying the adjusted sALP-levels results in a significant and independent prognostic impact of ALP, without eliminating any of the previously significant prognosticators (gender, tumour volume and serum methotrexate (Mtx) at 24 h) (Table 1).

Thus, our reanalysis supports the importance of alkaline phosphatase as reported by Bacci and Meyers [2–4]. Bone ALP increases during the growth-spurt at puberty and decreases to low levels in early adulthood. Calculation of relevant reference values according to gender and age is complicated and inaccurate, partly due to the measurement of total sALP as opposed to the bone-specific isoenzyme, and partly due to individual variations with regard to puberty and growth.

We have also performed a re-analysis of the data on sLDH at diagnosis, and the lack of a detectable association with prognosis is maintained. This conflicts with the Italian data, possibly due to the limited number of patients in the SSG VIII series.

In conclusion, we agree with Bacci and colleagues that sALP is an important prognostic factor for primary osteosarcoma. However, methodological difficulties restrict its predictive value.

As regards the effect of gender on outcome, our re-analysis confirmed female gender as a strong positive prognostic factor. This is a consistent finding in Scandinavian studies since the introduction of intensive chemotherapy, but was not observed in older series that applied inadequate or no chemotherapy. Female gender is linked to a better response and survival in several cancer diseases treated with chemotherapy such as lymphomas, acute lymphoblastic leukaemia (ALL), colorectal cancer and lung cancer [5]. In the SSG studies, the difference appears unrelated to the histological response which suggests a differential effect of chemotherapy at

Table 1
Multivariate analysis of metastasis-free survival

		HR	95% CI	*P* value
Gender	Male	4.1	1.78–9.74	0.001
Tumour volume	>190 ml	2.8	1.26–6.11	0.011
ALP	Elevated	3.2	1.49–6.62	0.003
Mean Mtx at 24 h	>4500	0.3	0.14–0.66	0.003

HR, Hazard Ratio; 95% CI, 95% Confidence Interval; ALP alkaline phosphatase; Mtx, methotrexate.

☆ doi of comment referred to doi: 10.1016/S0959-8049(03)00546-X

* Corresponding author. Tel.: +47-22-934000; fax: +47-22-934973.

E-mail address: sigbjorn.smeland@klinmed.uio.no (S. Smeland).

doi:10.1016/j.ejca.2003.08.019

the micrometastatic level in favour of females. As far as we are aware, this phenomenon has only been clearly demonstrated in Scandinavian patients, and is the subject of ongoing research within the SSG.

References

1. Smeland S, Muller C, Alvegard TA, *et al*. Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders. *Eur J Cancer* 2003, **34**, 488–494.
2. Bacci G, Longhi A, Ferrari S, *et al*. Prognostic significance of serum alkaline phosphatase in osteosarcoma of the extremity treated with neoadjuvant chemotherapy: recent experience at Rizzoli Institute. *Oncol Rep* 2002, **9**, 171–175.
3. Bacci G, Dallari D, Battistini A, *et al*. The prognostic value of serum alkaline phosphatase in osteosarcoma of the limbs. *Chir Organi Mov* 1992, **77**, 171–180.
4. Meyers PA, Heller G, Healey J, *et al*. Chemotherapy for non-metastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol* 1992, **10**, 5–15.
5. Gotay CC, Phillips PH, Cheson BD. Male-female differences in the impact of cancer therapy. *Oncology (Huntingt)* 1993, **7**, 67–74 [discussion 74, 77].