Annals of Oncology 6: 89–91, 1995.

Letters to the editor

Soft tissue sarcoma and hypercalcemia

Hypercalcemia is a common and potentially life-threatening complication of several diseases: 60%–80% of cases are caused by hyperparathyroidism and malignancy [1]. Hypercalcemia of malignancy (HM), 80% comprising multiple myeloma, breast, bronchus, head and neck and urogenital tract cancers, occurs in 15–20 per 100,000 persons in Western societies [2]. HM is very uncommon in soft tissue sarcomas (STS) and has been reported only in childhood. Here we describe two adult patients with STS who developed HM at various stages of their disease. Patient A is a 24-year-old male with a rhabdomyosarcoma of the right maxillary sinus with orbita destruction and positive lymph nodes for which he was treated with rhinotomia, lymph node dissection and irradiation. Fourteen months later he complained of fatigue, loss of appetite and weight, nausea, obstipation and continuous right chest pain. On physical examination he appeared ill, without dyspnea or orthostasis. He had post-irradiation hallmarks on the neck and pain upon pressure on the back of the right chest. Hemoglobin was 5.0 mmol/l, white blood count 4.1 10^9/l with a left shift in the differential. Platelets were 48 10^9/l, creatinine 143 umol/l, calcium 3.21 mmol/l, phosphate 1.1 mmol/l, albumin 41 g/l. He had a soft tissue mass at the eleventh costa without bone infiltration, and pleural enlargement and effusion on both sides. A bone marrow biopsy revealed metastasized sarcoma. ECG results were normal. After rehydration and treatment with APD four days 30 mg IV normocalcemia was obtained. He later developed pain in the right leg and, after exclusion of bone localisations, it was concluded that lymph node metastases in the lumbar plexus had caused it. Because of his poor condition he was found to be unsuitable for chemotherapy. At present he is alive with acceptable pain.

Patient B is a 20-year-old male who presented with general complaints similar to those of patient A and with a painful swelling in the right upper abdominal quadrant. He appeared ill with a slight orthostasis and an abdominal swelling in the right upper quadrant with an irregular aspect. His creatinine level was 127 umol/l, calcium 3.72 mmol/l, phosphate 0.70 mmol/l, albumin 40 g/l bilirubin 22 umol/l, alkaline phosphatase 351, gamma GT 433, ASAT 145 ALAT 81 an LDH 4511 U/l. ECG results were normal. On CT an enlarged liver with diffuse metastases and a retroperitoneal mass was discovered. Liver biopsy revealed leiomyosarcoma. He was rehydrated and treated with APD 30 mg for three days, which resulted in normocalcemia. His clinical condition improved considerably and he was treated with eight courses of adriamycin and ifosfamide according to the EORTC protocol. A complete remission was obtained and 18 months after diagnosis he is still well.

The sarcomas in both patients belong to the group of muscle tissue sarcomas (Patient A: rhabdomyosarcoma; striated muscle subtype. Patient B: leiomyosarcoma; smooth muscle subtype). In both cases the STS had metastasized. Thus, neither of them was suitable for local resection with or without (neo-) adjuvant radio- or chemotherapy. HM is an uncommon finding in STS. It occurs predominantly in childhood [3, 4]. Leblanc et al. [4] described four patients aged less than 15 years, with rhabdomyosarcoma with bone metastases. In all of them HM disappeared after chemotherapy, but then recurred, and the patients subsequently died. Hutchinson et al. [5] also reported an association between HM and sarcoma in both children and mice. Ascites sarcoma 180 (S180A), an in vitro transplantable tumor, released substances, which caused bone resorption similar to that in humoral HM (HHM) [6]. In patient A bone metastases were likely to be responsible for the hypercalcemia, based on the normal phosphate level and the observed bone marrow metastases despite the absence of radiological findings. We believe that in patient B, the hypercalcemia could be due to HHM, as the phosphate level was low and there were no clinical signs of bone metastasis. In this case the determination of parathyroid hormone-related protein (PTHrP) may have been helpful, as it has effects on the parathyroid receptor similar to those of parathyroid hormone (PTH). However, in neither of these two patients could the HM be fully attributed to either HHM or bone metastases.

To our knowledge HM in adult patients with STS is very rare, never before having been reported. In larger studies concerning the prevalence of HM, STS has never been found to be the underlying malignancy, whereas it may occur in osteosarcoma. The majority of symptoms associated with hypercalcemia such as weight loss, anorexia, polydispsia, fatigue, muscle weakness, nausea, vomiting and renal failure, were present in both patients. Nevertheless, there was a delay in the discovery of hypercalcemia because the complaints were not specific and were ascribed to disseminated malignancy, and because we were not unaware of the association between STS and HM. Thus, it is important to assess serum albumin and calcium in any patient with a malignancy and vague symptoms. The present cases demonstrate that this approach should not be restricted to patients with bone metastases or patients with malignancies, which are often complicated by HM.

G. Vreugdenhil,[1,2] P. H. M. de Mulder[2] & Q. van Hoesel[2]

[1]*Department Internal Medicine, Sint Joseph Hospital, 5500 MB Veldhoven;* [2]*Department Medical Oncology, University Hospital, Nijmegen, The Netherlands*

References

1. Lafferty FW. Differential diagnosis of hypercalcemia. J Bone Min Res 1991; 6 (Suppl 2): S51–S592.
2. Warrell RP. Metabolic emergencies. Hypercalcemia. In De Vita VT, Hellman S, Rosenberg S (eds): Cancer: Principles and Practice of Oncology. Philadelphia: J.B. Lippincott Co. 1993; 2128–40.
3. Gibbs J, Dillon MJ, Lang S et al. Indomethacin-responsive hypercalcemia associated with a renal sarcoma. Arch Dis Child 1990; 65: 1168–9.
4. Leblanc A, Caillaud JM, Hartman O et al. Hypercalcemia preferentially occurs in unusual forms of childhood non-Hodgkin's lymphoma, rhabdomyosarcoma and Wilms' tumor. Cancer 1984; 54: 2132–6.

5. Hutchinson RJ, Shapiro SA, Raney RB. Elevated parathyroid hormone levels in association with rhabdomyosarcoma. J Pediatr 1978; 92: 780–1.
6. Suzuki Y, Yamada S. Ascites sarcoma 180, an animal model of humoral hypercalcemia of malignancy, produces a factor (s) exhibiting potent bone resorbing activity without any parathyroid hormone-like activity. Bone Min 1991; 14: 1–13.

Adjuvant chemo-hormonal therapy with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) with or without medroxyprogesterone acetate for node-positive cancer patients. Update at 7-year follow-up

The Comprehensive Cancer Center Limburg trial 82-01 is a prospective randomized investigation of the value of the addition of high-dose medroxyprogesterone acetate (MPA) to CAF chemotherapy in patients with node-positive (N+) operable breast cancer (T_{1-3}, N_1). The results of 408 evaluable patients, after a median follow-up of 42 months, have been published in *Annals of Oncology* [1] and can be summarized as follows: high dose MPA ameliorates CAF side effects and reduces the risk of metastatic disease in elderly breast cancer patients. Patients ⩾60 years benefitted most from MPA treatment, in particular if freedom from distant metastasis was taken as endpoint (p = 0.02). Overall survival (OS) showed a significant advantage in patients ⩾55 years (p = 0.002). In this letter we report the updated results after a follow-up of 7 years.

After a median follow-up of 84 months the conclusions of the study remain unchanged. No differences in disease-free survival (DFS), distant-metastasis-free survival or OS were found for the patients as a whole (p-values were 0.12, 0.12 and 0.18, respectively). OS curves of all patients whether treated or not with MPA are shown in Fig. 1. Subset analysis revealed a significantly better DFS for the patient group aged between 40 and 60 years than for the group ⩽40 or >60 years (p = 0.002). This difference is MPA treatment independent.

Patients ⩾60 years showed a significantly longer DFS and OS when MPA was added to CAF chemotherapy (p-values 0.05 and 0.008, respectively) (Fig. 2).

By contrast, in the subgroup of patients <40 years, the addition of MPA to chemotherapy proved detrimental: the relative risk (RR) for relapse of breast cancer was 1.6 versus 1.1 for patients with and without MPA, respectively, while the RR in the group ⩾60 years was lower (0.7 vs. 1.0), in favor of the MPA-treated group.

In conclusion, this trial suggests a beneficial effect of MPA in combination with chemotherapy in elderly patients (⩾60 years). The beneficial effect may in part be explained by higher estrogen receptor (ER) levels in elderly breast cancer patients. In young breast cancer patients (⩽40 years) MPA added to adjuvant chemotherapy has a detrimental effect, possibly caused by its protective effect on ovarian function during CAF chemotherapy [2], which prevents CAF chemotherapy-induced ovarian ablation. An alternative explanation may be that MPA reduces the cellular ER and PgR content in breast cancer cell lines [3]. This down-regulation of ER content in pre-menopausal breast cancer patients could have a

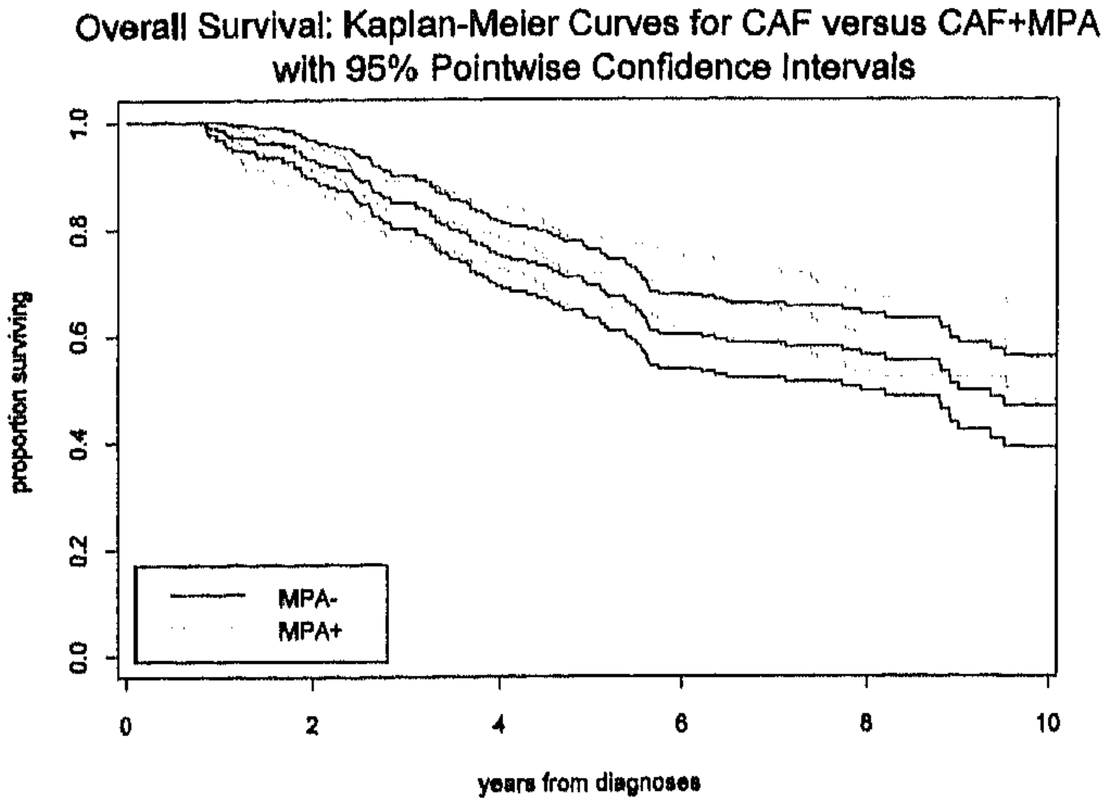

Fig. 1. Overall Survival (OS) curve for all node-positive patients in both treatment arms. No statistically significant differences between the two treatment arms (p = 0.12). For both survival curves 95% confidence bounds are drawn.

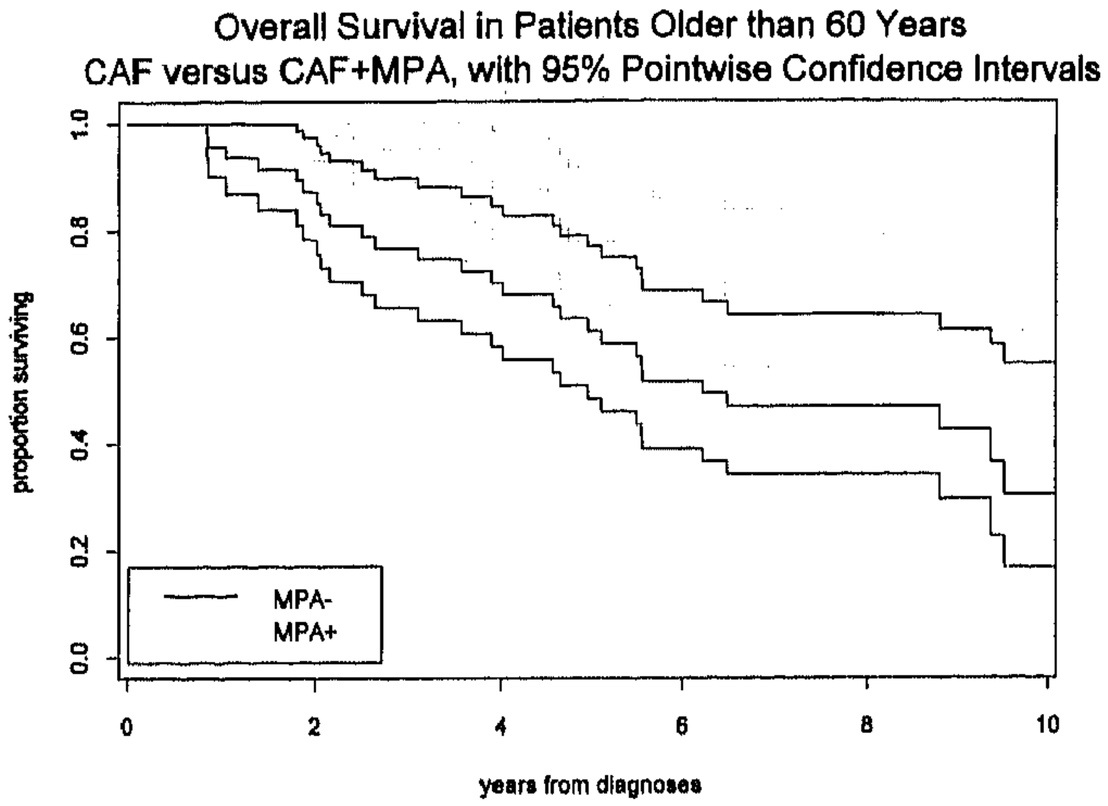

Fig. 2. Overall Survival (OS) curve for both treatment arms in patients ⩾60 and ⩽70 years. Differences in favor of the CAF + MPA treatment arm (p = 0.008). For both survival curves 95% simultaneous confidence bounds are drawn.

negative influence of endogenous estrogen on the tumor-cell cycle (lower percentage of tumor cells in the proliferative phase) causing a reduced effect of adjuvant chemotherapy on tumor cells in premenopausal patients.

The previously described bone marrow protective effect of MPA [1] is supported by two recent studies demonstrating in vitro that MPA causes a cell-cycle arrest of hematopoietic precursors which protects them from the toxicity of chemotherapy [4], and in vivo that MPA induces a mitotic arrest in hematopoietic stem cells [5].

The combination of MPA and chemotherapy deserves further exploration in postmenopausal breast cancer patients.

P. Hupperets,[1] J. Wils,[1] L. Volovics,[1] L. Schouten,[1] M. Fickers,[1] H. Bron,[1] H. Schouten,[1] J. Jager,[1] J. de Jong,[1] L. Beex,[2] H. Hillen[1] & G. Blijham[3]
[1]*Breast Cancer Study Group of the Comprehensive Cancer Center Limburg, Academic Hospital Maastricht, 6202 AZ Maastricht;* [2]*Department of Internal Medicine,*