Acta Oncologica Vol. 30 No. 2 1991

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ALKALINE PHOSPHATASE

A marker in prostatic cancer?

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Abstract

From reports in the literature the author concludes that alkaline phosphate is an unspecific marker in prostate cancer correlated to degree of bone involvement, response to treatment and survival.

Key words: Prostate cancer, alkaline phosphatase, survival.

The observation that total serum alkaline phosphatase might be elevated in prostate cancer patients actually preceded the establishment of acid phosphatase as marker for that disease (1). Alkaline phosphatase is considered a non-specific tumour marker, being neither organ—nor tumor specific. It has been widely used as a marker for tumors of the skeleton.

Measurement of total alkaline phosphatase includes a series of isoenzymes produced by various organs like liver, intestine, kidney, placenta, and bone. The most important ones seem to be the liver and bone isoenzymes. In 1976, Killian et al. (2) described a simplified method for measuring total alkaline phosphatase and its isoenzymes.

Using these methods Wajsman et al. (3) reported on alkaline phosphatase in 357 patients from the National Prostatic Cancer Project (NPCP), all with proven bone metastases. Three hundred and five had elevated total alkaline phosphatase levels—mainly owing to elevation of the bone isoenzyme fraction. Fifty-two had a normal level despite widespread bone metastases. However, of the 52 patients with normal total level of alkaline phosphatases, 22 had abnormal high levels of bone alkaline phosphatases, indicating a value of this isoenzyme to indicate extensive tumor load of the skeleton.

In the same paper (3) they also reported on 105 patients with metastatic disease where the alkaline phosphatase isoenzymes were correlated to clinical response. These patients had entered the National Prostatic Cancer Project studies to determine the value of different chemoterapeutic agents. The initial levels of both total and bone alkaline phosphatase (ALK-P), as well as the follow-up levels, were correlated to the response to therapy. The average time of observation was 18 months. Of the 105 patients 6 were considered to have partial response and these had the lowest total and bone ALK-P levels. Sixty-eight had progressive disease and these had the highest initial enzyme levels whereas 31 patients became stable and had enzyme levels in between the two other clinical categories. The difference in the initial serum levels of these 3 response categories of patients were significant with a p-value of <0.01.

Merrick et al. (4) reassessed the prognostic significance of skeletal scintigraphy in relation to other tests by extended follow-up of 220 patients. The survival of patients with a raised acid phosphatase at presentation was significantly shorter than that of those with normal values ($p < 0.01$). The difference was much more marked when considering alkaline phosphatase ($p < 0.001$). Multivariate analysis using the Cox's proportional hazards test showed that the alkaline phosphatase alone accounted for all of the differences in survival. None of the other factors was significant, given the alkaline phosphatase findings. Scintigraphy gave no additional information about prognosis in patients with a normal alkaline phosphatase.

The EORTC GU-group used data from their trials 30761 and 30762 for study of prognostic factors for

Presented at the Conference on Early Prostatic Cancer. The WHO Collaborating Centre for Urological Tumours, Karolinska Hospital, Stockholm, March 21–23, 1990.

Accepted for publication 22 September 1990.

duration of survival by multivariate analysis (5). Considering only tumor markers, their results showed that when PAP was twice the normal range in patients without metastases this was highly significant to indicate a shorter survival. More important in this context was the fact that for patients with metastatic disease, an increased alkaline phosphatase was significantly related to a shorter survival.

Killian et al. (6) studied the ability to predict progression for prostate specific antigen (PSA), prostatic acid phosphatases (PAP), serial acid phosphatases (ACP), and total alkaline phosphatase (ALK-P). One thousand and sixty-five serum specimens were collected from 130 patients during an 8-year period. They used a double-blind non-interventive method and employed sophisticated statistical techniques.

The first group had only localized cancer. Of these 79 patients with B2-C and D1 stage of disease, 40 progressed during the follow-up period. The estimated relative risk of progression in patients with elevated PSA levels was 3.25 times higher than for those who did not have an elevated PSA level. For elevated PAP levels the respective risk was 2.2 times. Only these two are significant markers of imminent progression for localized disease. Bone ALK-P, ALK-P and AcP were not significantly related to progression. Furthermore, elevated PSA levels were predictive of an increased risk 6 months prior to progression.

The second group had advanced cancer. Of these 51 patients, 21 presented clinical progression during follow-up. The estimated relative risk of progression for patients with elevated PSA was 8.6 times that of patients with normal levels. The corresponding figures for bone ALK-P and PAP were 5 and 2.95 respectively. These three markers were all significantly related to an unfavorable prognosis in advanced disease.

Overall, combining localized and advanced disease, the apparent order of prognostic reliability for disease progression was found to be PSA > PAP > bone ALK-P > AcP > ALK-P. Multivariate analysis was performed to see if the prognostic importance of the markers was additive. They showed that detection of a disease progression with the use of PSA was not augmented by the value of any additional marker.

In this short presentation only a few reports could be cited—there are certainly many others which deserve to be mentioned. From what has been reported it seems reasonable to conclude that alkaline phosphatase is valuable in advanced disease for indicating survival and progression.

Whatever alkaline phosphatase measurements might contribute, however, --- PSA probably will do better!

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