ONCOLOGY

Calmodulin in Osteogenic Sarcoma

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The content of calmodulin in homogenates prepared from various morphological variants of primary osteogenic sarcoma varies from 408 to 14,255 ng/mg total protein and is lowered by neoadjunctive chemotherapy. The 5-year incidence of metastases is lower when the calmodulin content in the tumor is >6000 ng/mg protein. At calmodulin content <6000 ng/mg protein, the occurrence of metastases is lower in patients receiving neoadjunctive therapy before surgery than in untreated patients.

Key Words: *osteogenic sarcoma; calmodulin*

Hormones and polypeptide growth factors play an important role in tumor growth [4-6]. Their effects on cells, tissues, and organs are realized via intracellular messengers [1,2].

Two major messengers of hormonal signaling have been identified: 1) the adenylate cyclase system generating the second messenger cyclic AMP and 2) transmembrane proteins determining Ca^{2+} influx ("slow" calcium channels).

The structure of "slow" calcium channels has been extensively studied. It was found that the effects of Ca^{2+} are realized via their binding to calmodulin (CM), a specific polyfunctional protein [2,3,7].

The aim of the present study was to determine calmodulin content of osteogenic sarcoma (OS) and examine the relationship between CM content, metastasizing, and duration of remission.

MATERIALS AND METHODS

Fifty-eight patients with primary OS (38 men, 20 women, and 26 adolescents under 18) were enrolled in the study. In 96.5% of the patients the tumor was located in long tubular bones. Clinical and roentgenologic diagnoses were confirmed by histological examination according to the international classification [6].

Typical OS was diagnosed in all patients: osteoblastic in 29, chondroblastic in 6, telangiectatic in 5, fibrohistiocytic in 8, highly differentiated in 3, and small-cell in 7. Eighteen patients received intra-arterial chemotherapy before operation. During the postoperative period 45 patients received adjunctive therapy: 22 patients were treated with adriamycin and 22 patients were on the CAF regimen. Other patients received no therapy after the operation.

Calmodulin content in tumor homogenate was measured by radioimmunoassay using Amersham kits.

The results were analyzed using special statistical software for medical research.

RESULTS

The CM concentration in OS varies in a wide range: from 408 to 14,255 ng/mg protein, being lower in men (3127.7±1117.0 ng/mg protein) and women (4408.1±684.0 ng/mg protein) given neoadjunctive chemotherapy than in untreated patients (respec-

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tively, 5886.9±116.8 and 5869.0±618.0 ng/mg protein).

We examined the relationship between CM content and survival rate irrespective of chemotherapy. For this purpose the patients were divided into two groups: group I consisted of 21 patients with CM concentration in the tumor >6000 ng/mg protein and group II included 37 patients with CM concentration in the tumor <6000 ng/mg protein.

In group I, 10-year survival rate without tumor dissemination was 76.1% (16 patients). It should be noted that the patients which did not die from generalization of the process within the first 3 years were alive during the entire observation period.

For the majority of group II patients the prognosis was unfavorable: 10-year survival rate was only 43.2% (16 patients out of 37).

Ten-year survival rate in group I patients was higher in women (62.5%, 5 out of 8) than in men (33.3%, 4 out of 13). It should be noted that metastases appeared after 2 years in 50% women and in 25% men. In group II patients, 10-year survival rate was 27.9% for women and 24.0% for men.

Prognosis concerning the disease progression at CM content in the tumor >6000 ng/mg protein was better for men than for women. There were no statistically significant differences in the prognosis for men and women with CM concentration <6000 ng/mg protein.

The relationship between 10-year survival rate and tumor CM content was analyzed separately in 26 children and adolescents under 18. In group I (>6000 ng/mg protein), one out of 9 patients died 4 years after surgery, the 10-year survival rate being 88.8%. In group II (<6000 ng/mg protein), 10 out of 17 patients died within 5 years, and the 10-year survival rate was 41.1%. The difference in the 10-year rates in patients with CM contents in the tumor higher and lower than 6000 ng/mg protein was statistically significant (p=0.0048).

Thus, the occurrence of metastases during several years after surgery is lower in patients with CM content in the tumor >6000 ng/mg protein. This tendency is more pronounced in children and adolescents.

We analyzed the effect of neoadjunctive chemotherapy on the occurrence of lung metastases of patients with OS taking into account the CM content of OS. Eighteen patients received chemotherapy before operation. In 1 out of 4 patients with CM content >6000 ng/mg protein lung metastases appeared within the second year after the start of therapy. In 9 out of 14 patients (64.2%) with CM contents <6000 ng/mg protein lung metastases were revealed within two years from the start of therapy. Among 16 patients with CM content >6000 ng/mg protein who did not receive neoadjunctive therapy metastases were revealed in 8 patients (50%) within 5 years after operation, while at CM content <6000 ng/mg protein metastases appeared in 16 out of 20 patients (80%) within 5 years from the start of therapy.

The relationship between CM content in primary tumor and duration of remission was studied in patients (n=45) given chemotherapy during the postoperative period. Twenty-three patients were treated with adriamycin and 22 patients were on the CAF regimen. Among adriamycin-treated patients nine were with CM content >6000 ng/mg protein; in 5 of them (55.5%) tumor dissemination occurred within the first 5 years. In 9 out of 14 patients (64.2%) with CM content <6000 ng/mg protein metastases appeared within the same period. Eight patients on the CAF regimen had CM content >6000 and 14 patients <6000 ng/mg protein. In the first subgroup metastases appeared in 4 patients (50%), and in the second subgroup in 10 patients (71.4%) within 5 years of observation.

From our findings it can be concluded that there is a relationship between the CM content in OS and duration of remission.

- In patients with OS with the CM content >6000 ng/mg protein the occurrence of metastases within the first 5 years from the beginning of treatment is lower and remission is longer.
- Preoperative chemotherapy decreases the occurrence of metastases within the first years from the beginning of treatment in comparison with untreated patients with CM concentration in primary tumor <6000 ng/mg protein.
- The CM content can be employed as an indicator of "metastasizing activity" of osteogenic sarcoma and, consequently, as a factor of the disease prognosis.

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