MONITORING OF BONE RESORPTION AND BONE FORMATION IN MULTIPLE MYELOMA

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The article deals with the clinical value of monitoring of serum markers of osteoresorption (ICTP) and bone formation (PICP) in multiple myeloma. In a group of patients treated by conventional chemotherapy and group of patients treated by high dose chemotherapy with autologous peripheral blood stem cell transplantation (APBSCT).

INTRODUCTION

Multiple myeloma (MM) is caused by malignant proliferation of plasma cells. Increased osteoresorption plays important role in MM. Osteolytic lesions and osteoporosis is one of the clinical manifestations of MM which causes serious morbidity. Morphology of bone involvement can be assessed by imaging technics as X-ray, MRI and bone densitometry DEXA. The bone involvement is induced by uncoupling of two essential processes – bone resorption and formation which are under normal circumstances balanced. The activity of bone resorption and formation is reflected by some biochemical markers.

One of specific biochemical markers of osteoresorption is ICTP (cross-linked carboxyterminal telopeptide of type I collagen) which reflects degradation of bone. PICP (carboxyterminal propeptide of type I procollagen) reflects synthesis of bone matrix^{1,2} can be used as an indicator of bone formation.

Beta 2-microglobulin is an expression of tumor burden and correlates with the Durie-Salmon staging system for assigning prognosis. LDH is related to intrinsic malignancy. Both these markers were used in this study as instrument for evaluation of activity of the malignant process.

Levels of bone markers ICTP and PICP are changing during course of disease^{3,4}.

THE AIMS OF OUR STUDY

Were to investigate evolution of biochemical markers of osteoresorption (ICTP) and bone formation (PICP) during the course of disease, find relations between these markers and

- markers of tumor mass: serum beta 2-microglobulin, monoclonal immunoglobulin – MIG, Hb, serum-Ca, percent of infiltration of bone marrow by plasma cells and presence of X-ray detected osteolytic lesions..
- markers of intrinsic malignancy: serum lactate dehydrogenase – LDH, thymidine kinase, CRP, s-albumin,
- evaluation of Kaplan-Meier curves of survival
- evaluation of ICTP and PICP markers during course of disease in patients treated by conventional chemotherapy and in patients treated by high dose chemotherapy with APBSCT.

METHODS

Patients: 73 patients with multiple myeloma (33 males, 40 females), age median 60 years with an age range of 38 to 78 years. 47 patients were treated by conventional chemotherapy (M2, Cy-VAD) and 28 patients were treated by high dose chemotherapy with autologous stem cell transplantation (APBSCT). All patients were treated by bisphosphonate-clodronate 1600 mg p. o. daily.

ICTP and PICP were measured in serum by RIA method Orion diagnostica, Finland.

Normal levels of ICTP is 1.8–5.0 ng/ml, normal levels of PICP is 50–170 ng/ml in females and 38–200 ng/ml in males⁶. Beta 2-microglobulin was evaluated in serum by RIA method, normal levels are up to 2.4 ng/ml. Serum LDH was evaluated, normal level 3.8–7.8 ukat/l.

Serum levels of ICTP and PICP were compared with serum levels of beta 2-microglobulin and LDH. Patients were followed for the period of one to three years. Statistical analysis was done by Pearsons test and U-test.

RESULTS

Marker of osteoresorption-serum ICTP was 6.9 ± 2.6 micrograms/l, range 2.6–30 micrograms/l).

Serum ICTP (more than 5 microgram/l) was elevated in 70% of patients. Pretreatment ICTP serum levels showed a parallel increase with the stage of the disease according to Durie-Salmon classification. (Fig. 1) Osteolytic activity (ICTP) was increased in progressive disease and in non-responders to chemotherapy. (Fig. 2).

The level of beta 2-microglobulin was increased in the same group.

In patients after high dose chemotherapy with APBSCT was ICTP dropping slowly during few months (Fig. 3). ICTP at time of diagnosis was 6.9, dropping to 5.8 after transplantation.

It shows that osteolytic activity persists even after high dose chemotherapy with APBSCT. Beta2-microglobulin was decreasing much earlier after high dose chemotherapy with APBSCT than ICTP.

Serum ICTP levels correlate with serum beta 2-microglobulin ($r 0.24$, $p < 0.04$). There was also strong correlation ICTP with s-creatinine ($r 0.32$, $p < 0.007$), ICTP and infiltration of bone marrow with plasma cells ($r 0.5$, $p < 0.007$). ICTP with LDH ($r 0.37$, $p < 0.003$), ICTP with CRP ($r 0.52$, $p < 0.03$).

Increased serum level of ICTP correlate with presence of X-ray detected bone lesions and stage of disease according Durie-Salmon.

No correlation was found between serum ICTP and age, Hb, MIG, S-Ca, PICP, S-albumin and S-TK. We did not find correlation of ICTP with MRI pattern of bone marrow.

Survival (months) correlated to serum ICTP is shown in diagram (Fig. 4).

Marker of bone formation serum PICP was generally within the reference limits, increased only in 10% of patients (121 ± 39 , range 42–508 micrograms/l).

The correlation was found between PICP and LDH ($r 0.43$, $p < 0.001$), and PICP and infiltration of bone marrow by plasma cells ($r 0.39$, $p < 0.007$).

DISCUSSION AND CONCLUSION

Majority of MM patients (70 %) in this study had elevated values of serum ICTP. This observation may be explained by increased osteoclastic activity causing resorption of bone matrix, degradation of type I collagen and liberation of ICTP into circulation. ICTP is also elevated in renal insufficiency^{5,7}, which is common among MM patients due to kidney involvement.

Increased level of ICTP were found in patients with progressive or relapsing disease.

Increased level of ICTP was accompanied by increased beta2-microglobulin – a marker of tumor burden – and by stronger infiltration of BM by plasma cells.

We found relation of ICTP to markers of intrinsic malignancy – LDH and CRP. These data show that

Fig. 1. ICTP and stage of multiple myeloma

Fig. 2. ICTP in responders and non-responders
ICTP increasing in non-responders

Fig. 3. ICTP dropping after high dose chemotherapy with APBSCT

Fig. 4. Survival according serum ICTP at the time of diagnosis

ICTP serum levels increase with advanced disease stage. In multiple myeloma an elevated ICTP serum level is an adverse prognostic factor for survival. Increased level of ICTP has prognostic significance for life expectancy of MM patients.

Serum levels of ICTP seem related to bone turnover and provide further information about myeloma activity particularly in normocalcemic patients.

Marker of bone formation PICP has but a limited value according results of this MM patients group.

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