Diagnostic Usefulness and Changing Value during Irradiation of Bone Metabolic Markers for Metastatic Bone Tumor

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Key Words : Bone metabolic marker (BMM), Metastatic bone tumor (MBT), ICTP, PICP, Irradiation

ABSTRACT

Objective: We examined the efficacy of Pyridinoline-cross-linked C-terminal telopeptide of type I collagen (ICTP) and C-terminal propeptide of the type I procollagen (PICP), as bone metabolic markers (BMM) that reflect the effects of radiotherapy in patients with metastatic bone tumors (MBT).

Method: One-hundred eight patients who had had malignant tumors and been suspected of developing MBT were measured for ICTP and PICP. Ninety six patients with recognized MBT and 12 patients without MBT were evaluated for the diagnostic accuracy of MBT. Out of the 96 cases, 49 received radiotherapy and were measured for ICTP and PICP before and after the treatment. The 49 cases were divided into 25 cases (Com group) that had all of the MBT irradiated and 24 cases (InCom group) that could not have all sites irradiated. Increase ratios from before to after the radiotherapy were compared between ICTP and PICP.

Results: In the 96 patients with MBT, both ICTP and PICP were observed to be significantly high. Diagnostic accuracy was 81.5% for ICTP, and 61.6% for PICP. InCom group showed an increase in ICTP by about 25% while no significant change was observed in the Com group.

Conclusion: BMM has diagnostic significance in patients with MBT. Performing radiotherapy to every osseous lesion results in a decline or leveling-off of ICTP.

INTRODUCTION

We conduct radiotherapy on patients with bone metastasis, expecting a pain-relief effect, and its treatment effect is evaluated based on reduction of subjective pain [1,2].

Before therapy, sites and numbers of metastatic bone tumors (MBT) are evaluated by bone scintigraphy. After therapy, metastatic bone foci sometimes show temporary accumulation and build-up called “flare phenomenon” in normal bone regeneration [3], and normalization takes place after several months. It is difficult to accurately measure size and range of metastatic tumors inside bone even by using such imaging as computed tomography (CT) and magnetic resonance imaging (MRI), and
the effect of therapy cannot be confirmed based on objective imaging.

The treatment effect for malignant tumors is judged by evaluating the size using such imaging as CT and MRI, and confirming the decrease of tumor markers. Regarding MBT, however, it is difficult to differentiate recurrence from primary foci and MBT recurrence, with tumor markers as the only basis. Also, after radiotherapy, bone metastasis around the treated area sometimes expands, resulting in a need for change in the irradiation field; or new MBT occurs, requiring re-treatment. For such occasions, bone scintigraphy and other imaging evaluation are needed. Therefore, we felt the need of indices that reflect treatment effects, like tumor markers, during and immediately following radiotherapy.

We focused on bone metabolic markers (BMM) that diagnose BMT, and studied whether or not they reflected efficacy even during and immediately following therapy. BMM consists of osteoclastic markers, which reflect bone resorption, and osteoblastic markers, which reflect bone regeneration; in either case, metabolites are present in blood and urine. BMM in urine is susceptible to effects from inherent bone metabolism, so it is necessary to regulate collection time (early morning, within a few hours after getting up) [4,5].

On the other hand, BMM in the blood is relatively insusceptible to normal bone metabolism. As such, we decided to study ICTP as a bone resorption marker and PICP as a bone hardening marker, from among BMM in the blood.

There are reports that studied changes in BMM in therapies other than radiotherapy for MBT from breast cancer, prostate cancer, and lung cancer, and concluded that BMM reflects the treatment effects [6], but we could not find any report in which measurements were made before and after radiotherapy and the effect of the treatment was evaluated. BMM is not a substance produced from the tumor itself, unlike a tumor marker, but is an intermediate substance metabolized from normal bone; the effect of radiotherapy on normal bone metabolism is not known. It is ethically difficult to conduct radiotherapy to the bone of a patient with no bone metastasis and study changes of BMM. Further, even if a bone metastasis marker is measured immediately after the therapy, it is unclear if it quickly decreases / normalizes. As such, we classified patients into a treatment group in which all MBTs were included in the irradiation field, and treatment effect is predicted to be good; and another treatment group, in which all MBTs were not included, and treatment effect is predicted to be poor; measured BMM before and after radiotherapy, and studied what kind of changes in BMM showed treatment effects and if measurements immediately following therapy are meaningful for judging treatment effects, like tumor markers.

**MATERIALS and METHODS**

**Patients**

1) Diagnostic usefulness of BMM: During the period between May of 1997 and April of 1999, we studied 108 patients who had a malignant tumor and suspected MBT, whose presence or absence of MBT was confirmed by bone scintigraphy, etc. No patient had bone metabolic diseases, such as hypercalcemia, kidney failure, or hyperparathyroidism. We measured ICTP and PICP in 96 cases in which MBT was noted, and 12 cases in which MBT was not noted.

We classified the 96 cases that had MBT according to the number of MBTs. We rated one osseous lesion as grade 1; 2 to 5 osseous lesions as grade 2; and 6 or more lesions as grade 3 (Table 1).

2) Changes in BMM due to radiotherapy: Out of the 96 patients who had MBT and were applicable to radiotherapy due to pain, we measured BMM within one week before and after start and end of radiotherapy in 49 patients. We classified MBT(+)

<table>
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<tr>
<th>Age (years)</th>
<th>MBT(+)</th>
<th>MBT(-)</th>
</tr>
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<tbody>
<tr>
<td>61.9±10.7</td>
<td>57.6±13.3#</td>
<td></td>
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</table>

| Mle/Female | 56/40 | 2/10 |

<table>
<thead>
<tr>
<th>Origin (cases)</th>
<th>Lung</th>
<th>Breast</th>
<th>Liver</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>33</td>
<td>23</td>
<td>14</td>
<td>26*</td>
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<table>
<thead>
<tr>
<th>grade (cases)</th>
<th>1 (n=1)</th>
<th>2 (&lt;n&lt;6)</th>
<th>3 (n ≥ 6)</th>
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<td></td>
<td>37</td>
<td>27</td>
<td>32</td>
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Kne (5), Prostate (3), Neck (2), Colon (2), Bile duct (2), Esophagus (2), Stomach (2), Urinary bladder (2), Malignant lymphoma (1), Multiple myeloma (1), Pancreas (1), Thymus (1) and unknown (2)

| **Table 1** Classification of MBT cases and non-MBT cases according to age, gender, primary foci, and extent. No significant difference in age (#). |
Bone metabolic markers on irradiation

The blood levels of ICTP and PICP were measured respectively using Pyridinoline ICTP "Chugai" and Procollagen PICP "Chugai" (Orion Diagnostica, Finland). The cut-off values were set at 4.5 ng/ml for ICTP and 160 ng/ml for PICP.

Osseous lesions were judged by performing bone scintigraphy in every case, and diagnosis was made by two or more radiologists. The cases in which judgment were difficult by bone scintigraphy, diagnosis were made comprehensively using other diagnostic imaging.

Establishment of Irradiation

Radiotherapy was performed on patients who had pain from MBT, after the above diagnosis. The irradiation field was decided by radiologists using an X-ray simulator (Toshiba LX40, Japan), and then radiotherapy was performed using radiotherapy equipment (Toshiba Mevatoron KD2-50, Japan).

BMM of Increase Ratio during Irradiation

Increase ratios of bone metabolic markers during radiotherapy were calculated by dividing the values of ICTP and PICP after the therapy (post value) by the values before the therapy (pre value), and correction was made according to measurement periods, to calculate increase ratios per 30 days.

Increase ratio = post value / pre value × 30 / measurement period (days)

Statistical analysis

Measured values were indicated as mean±SD. Respective measured values were tested using statistics software Stat-View (SAS Institute Inc. Fulfillment Services Department SAS Campus Drive Cary, NC 27513-2414); Non pared t-test was used between two groups; analysis of variance was used among three groups, and then Post-Hoc test was conducted using Fisher’s PLSD method.

p<0.05 was regarded as statistically significant.

RESULTS

Diagnostic usefulness of BMM

There was no age difference between the 96 cases that had MBT and the 12 cases that did not have MBT. For both ICTP and PICP, MBT patients showed significantly higher values.

In the three groups classified according to MBT extent, out of the 96 cases with MBT, ICTP showed no difference among the three groups (ANOVA; F(2, 93)=0.076, p = 0.9267). PICP showed significantly higher values according to grades (ANOVA; F (2, 93) =3.552, p=0.0326), with a significant difference between grade 1 and grade 3 (p=0.0123) (Table 3).

As to accuracy of the diagnosis, when the cut-off values are set at 4.5 ng/ml for ICTP and 160 ng/ml for PICP, ICTP showed 86.5% for sensitivity, 41.7% for specificity and 81.5% for accuracy, while PICP respectively 46.9%, 91.7%, 61.6%.

Table 2  Classification of Com group and InCom group according to age, gender, irradiation dose, measurement period, and primary foci.

<table>
<thead>
<tr>
<th></th>
<th>Com group</th>
<th>InCom group</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62.5±12.6</td>
<td>59.8±10.4</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>15/12</td>
<td>13/11</td>
</tr>
<tr>
<td>Irradiation dose (Gy)</td>
<td>45.4±8.5</td>
<td>42.4±6.8</td>
</tr>
<tr>
<td>Term (days)</td>
<td>36.8±12.1</td>
<td>39.4±19.1</td>
</tr>
<tr>
<td>Origin (cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>10*</td>
<td>5**</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

* Rectum (4), Bile duct (2), Malignant lymphoma (1), Neck (1) and unknown (1)
** Esophagus (1)

Table 2  Classification of Com group and InCom group according to age, gender, irradiation dose, measurement period, and primary foci.

Measurement Materials of BMM and Diagnosis of MBT

The blood levels of ICTP and PICP were measured respectively using Pyridinoline ICTP “Chugai” and Procollagen PICP “Chugai” (Orion Diagnostica, Finland). The cut-off values were set at 4.5 ng/ml for ICTP and 160 ng/ml for PICP.

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InCom group in terms of pre ICTP value and pre PICP value. As to ICTP increase ratio, Com group showed a significantly higher value (p=0.0044), but no difference was noted between the two groups regarding PICP increase ratio (p=0.7037) (Table 4).

Also, the courses of BMM measurements in two cases for 80 days, including the treatment period, are shown in the graph. One case is a 78 year-old male with lung cancer metastasized to the cervical vertebrae (grade 2), in Com group (Fig.1). ICTP, which initially showed a normal value, increased during the course, and bone scintigraphy found two bone metastases in the cervical vertebrae. In the site, 34Gy radiotherapy was performed, and retesting after the treatment period showed a decrease in ICTP, and re-measurement after 15 days showed an increase that leveled off, and symptoms did not reoccur.

The other case is a 51 year-old female with breast cancer, accompanied by multiple bone metastases (grade 3), in InCom group. 40Gy radiotherapy was performed only on the dorsal vertebra where she had pain, but ICTP continually increased during the course, and pain occurred in another site (lumbar vertebra) 40 days after completion of treatment, resulting in a need for more radiotherapy (Fig. 2).
DISCUSSION

Previous studies on BMM showed its usefulness in diagnosing lung cancer, breast cancer, and prostate cancer, which tends to be accompanied by MBT [7-9], but no patients subject to radiotherapy were included. In this study, patients with various MBTs are included. Because eight out of 12 cases with no MBT were patients with breast cancer, there was a gender difference from patients with MBT. The reason is considered to be that there were only a few prostate cancer patients, meaning males, who required radiotherapy.

In the study on MBT diagnosis accuracy, we used the BMT cut-off values recommended in the kit: 4.5 ng/ml for ICTP and 160 ng/ml for PICP.

As to ICTP, sensitivity was 86.5% and specificity was 41.7%. In the similar study on diagnosis ability, KOIZUMI et al. reported ICTP showed sensitivity was 48.6% and specificity was 91.6%, for all patients, with cut-off value at 4.9ng/ml [7]. In the lung cancer cases, however, sensitivity is higher than all patients. And in the prostate cancer cases, sensitivity is lower and specificity is higher than all patients. So, ICTP showed different sensitivity according to primary tissues. As to PICP diagnosis ability, sensitivity was 17.6%, and specificity was 96.1% for all patients. In the lung and prostate cancer, PICP showed lower sensitivity and high specificity than ICTP. In our study, PICP showed high specificity than ICTP. As such, we considered that, in using BMM, diagnostic ability is improved by first measuring PICP, which shows high specificity, and then measuring ICTP in cases with a normal range. When evaluation was made in such procedures, sensitivity slightly improved in cases in our study.

BMT extent needs to be classified according to occurrence sites and sizes, but it is difficult to measure volume of metastatic tumors in bone tissues by diagnostic imaging or bone scintigraphy. As such, classification was conducted based on number of tumors using bone scintigraphy as a substitute. For BMT extent, the EOD (extent of disease) score, which is used for BMT of prostate cancer, is known [10]. We did not use EOD scores, because we study patients receiving radiotherapy that are not limited to prostate cancer patients. Instead, we used a classification method using three grades, because of classification based on whether or not osseous lesions can be included in the irradiation field. The result showed no significant differences among grades in terms of measured values of ICTP, while PICP showed higher values according to grades. In a report using the same classification as in our study, ICTP showed higher values according to extent of bone metastasis in breast cancer, lung cancer, and prostate cancer, while PICP showed higher values in prostate cancer [7]. In our study, the number of cases was small when classified by tissues and number of metastases, and statistical evaluation was therefore difficult.

In the study on diagnostic significance mentioned earlier, fluctuation of diagnosis accuracy of ICTP according to tissues was considered to be large, while that of PICP was small, which we did not think contradictory to the fact that PICP only showed measured values according to extent in the group of cases that include various primary tissues as in our study. Furthermore, we felt the need of use according to respective primary tissues of bone metastases, as with other tumor markers, when ICTP is used.

In the study that compared increase ratios before and after radiotherapy to see if BMM reflects the effect of the therapy, ICTP showed a higher value in InCom group than in Com group, indicating that the increase ratio is reduced by radiotherapy. This result suggests that performing radiotherapy to every osseous lesion, even during a short period of about one month, results in a decline or leveling-off of ICTP. We felt a possibility of predicting the effect of treatment, without decline to normal values as with tumor markers, and without waiting for regeneration of bone tissues several months later as with diagnostic imaging; and a possibility of providing beneficial information for determining or changing treatment policy. There is a report that over-time measurement revealed ICTP increases in cases with MBT [8]. And bone scintigraphy has the highest diagnostic value in diagnosing bone metastasis from lung cancer, but BMM is also useful in screening and course observation [11]. Similarly, we considered that BMM is useful in judging effects before and after radiotherapy, much like judging effects in other therapies.

ARUGA et al. reported two cases with bone metastasis from lung cancer, in which BMM (ICTP) course was observed for one year. In one case with multiple bone metastases for part of which radiotherapy was performed, ICTP continually increased after the therapy, up to four times the normal value in one year. In the other case with single bone metastasis, ICTP normalized in about four months after radiotherapy and stayed around the upper limit of normal value [12]. As to the two cases that were observed for 80 days in our study, ICTP increase was stopped by radiotherapy in one case in Com group - though ICTP did not normalize, bone metastasis was considered to have been controlled
in this case; in the other case, in InCom group, ICTP continually increased even after radiotherapy, requiring another therapy. We considered it possible to obtain signs of recurrence of bone metastasis, by observing the course of BMM over a long term.

In this study PICP increase ratio did not show a certain tendency. However, there is a report that PICP shows higher values as the number of bone metastases increases as in our study and that PICP reflects BMT’s activity, correlating to the treatment effect on breast cancer [13]. In our study we studied the increase ratio during a relatively short term of radiotherapy lasting about one month, and we considered that BMT’s activity could be reflected in a longer period. Also, as to the two cases whose courses were followed, PICP stayed within a normal range in one case with lung cancer, while PICP continually increased as ICTP did in the other case with breast cancer. PICP was also considered to possibly indicate the course of bone metastasis, according to primary tissues.

In our study we could measure only two types of BMMs, but other studies in which BMMs other than ICTP were used reported that PINP is useful for lung and breast cancer [14,15], and NTx is more useful than ICTP for lung cancer [16]. We deduced that in the future a combination with other BMMs will enable more accurate judgment of treatment effects and grasping of medical conditions of patients with metastatic bone tumors, resulting in avoidance of frequent imaging tests and reduction of physical and financial burden. Even among patients with MBT, BMMs that increase vary according to primary tissues, and periods that show treatment effects vary according to BMM types, so we considered that their evaluation requires caution.

CONCLUSIONS

In patients with metastatic bone tumors, ICTP has high sensitivity and PICP has high specificity. Furthermore, PICP showed higher values according to increases in MBTs, regardless of the type of primary tissues, while ICTP showed variation according to tissues. We could speculate that the effect of radiotherapy is good in patients with bone metastasis unless ICTP does not increase during the therapy. Based on these, we considered that monitoring of BMM is useful for grasping treatment effects like tumor markers, indicating a possibility of reducing patients’ physical and financial burden.

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Received February 5, 2007
Accepted July, 18, 2007