Comparison of Bone Scan with Carbohydrate Antigen 15-3 for Evaluation of Bone Metastasis of Breast Cancer

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Abstract: This study aimed at comparing the bone scan and CA15-3 titer in patients with breast cancer for evaluation of bone metastasis. Thirty five patients with definite diagnosis of breast cancer were evaluated in Tabriz Imam Khomeini Hospital from 2007 to 2008. Bone scan (99 mTc-MDP) performed in all patients. The serum CA15-3 was measured by ECLIA method. The increased level was considered as >30 U mL⁻¹. The serum level of CA15-3 was compared between the patients with and without bone metastasis, as well as its correlation with the extent of bone involvement. Thirty five patients with the mean age of 51.69±10.77 (34.81) years were enrolled in the study. According to bone scan results, 24 (68.8%) patients revealed bone metastasis. The mean level of serum CA15-3 was significantly higher in patients with bone metastasis than patients without metastasis (26.37±4.74 U mL⁻¹ vs. 19.09±1.99 U mL⁻¹, p<0.001). There was not significant relation between the serum level of CA15-3 and the extent of bone metastasis (rho = -0.063, p = 0.769). Coordinates of the curve study yielded a cut-off point >21.8 U mL⁻¹ for the serum level of CA15-3 in our patients, with a sensitivity and specificity of 91.7 and 91%, respectively. Serum level of CA15-3 is higher in the patients with bone metastatic breast cancer; however, the recommended cut-off point might not be suitable for Iranian patients. Further studies with large sample sizes are recommended.

Key words: Metastasis, scintigraphy, tumor marker, oncology

INTRODUCTION

Tumor markers are frequently used for screening and monitoring in oncology. Carbohydrate antigen 15-3 (CA 15-3) is a tumor marker commonly used in the screening, early detection and monitoring of treatment for breast cancers (Velaurumath et al., 2008; Agyei Frempong et al., 2008; Uehara et al., 2008). Significant differences in CA 15-3 expression levels between those in benign tumors and those in stage III and IV disease have been reported. There was a positive correlation between CA 15-3 levels and patient prognosis (Uehara et al., 2008).

Breast cancer is a disease that commonly metastasizes to bone, increasing morbidity, mortality and health service costs (Cook and Fogelman, 1999; O'Brien et al., 1992, Gedik et al., 2006). The 99 m technetium (99 mTc) diphosphonate bone scan historically has played a significant role in the evaluation of skeletal disease and continues to be one of the most clinically used investigations in the staging and follow up of breast cancer patients (Cook and Fogelman, 1999; O'Brien et al., 1992). The detection of bone metastasis has both prognostic and therapeutic significance and early detection in the asymptomatic case may alert the clinician to the possible complications inherent in skeletal destruction (O'Brien et al., 1992; Gedik et al., 2006).

CA15-3 is a circulating human breast tumor associated antigen defined and assayed by two monoclonal antibodies (O'Brien et al., 1992; Estrada-Sánchez et al., 2003; Ruibal et al., 2006). The CA15-3 levels are known to correlate well with the disease stage in breast carcinoma (Estrada-Sánchez et al., 2003; Nicolini et al., 1999, 2003; Gion et al., 2001; Tomlinson et al., 1995). However, its value as an indicator or predictor of metastatic bone disease has yet to be fully elucidated. The aim of this study was to evaluate the reliability of CA15-3 as a marker of secondary bony deposits in breast cancer patients.

MATERIALS AND METHODS

A descriptive analytic study was performed on patients with breast cancer presenting to

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Radiology-Oncology Department and Nuclear Medicine Departments of Tabriz Imam Khomeini Hospital from 2007 to 2008. Thirty five consecutive patients with definite histopathologic diagnosis of breast cancer and bone metastasis certified by bone scintigraphy were selected for evaluation of bone scan findings and serum CA15-3 level.

The patients underwent bone scan 3-4 h following intravenous injection of 15-20 mCi of technetium 99 m methylene diphosphonate (99 mTc-MDP) using a gamma camera equipped with a low energy, high resolution collimator (General Electric, Infinia and ADAC, Philips). The photospeak was centered at 140 keV with a 20% window. The bone scans were evaluated by 2 experienced nuclear medicine physicians. One milliliter venous blood was sampled from patients and sent to laboratory for measurement of serum CA15-3 by electrochemiluminescence (ECLIA). Bone scintigraphy was considered as gold standard for diagnosis of bone metastasis in patients with breast cancer. Elevated serum level of CA15-3 was considered if more than 30 U mL⁻¹.

All patients signed informed consent and they did not pay any additional cost for participant in this study. The studied variables were age, site of bone involvement, area of bone involvement, serum level of CA15-3 and abnormal levels of CA15-3. New cut-off point for CA15-3 was determined using ROC diagram.

The collected data were expressed as Mean±SD and number and percentage. Statistical analysis was made by SPSS 15 statistical software. The quantitative variables were compared by Student t-test (independent samples) or Mann-Whitney U-test. Also, qualitative (Categorical) variables were compared by Contingency tables using Chi-Square test or Fisher's Exact Test. Correlation was assessed by Spearman's rho coefficient. Suitability of test was assessed by Hosmer and Lemershow test. New cut-off point was determined using ROC diagram and coordinates of the curve. In all instances, p = 0.05 were considered statistically significant.

**RESULTS**

We studied 35 patients with breast cancer in two Metastatic (Group Y) including 24 cases (68.6%) and Non-metastatic (Group N) including 11 cases (31.4%). The age range of patients was 34-81 years, with average age of 48.7±8.87 years. These measures for Groups Y and N have been showed in Table 1. The differences between groups were not statistically significant (p = 0.278).

Table 2 shows the distribution of regional involvement of bone metastasis in studied patients.

<table>
<thead>
<tr>
<th>Bone</th>
<th>No.</th>
<th>%</th>
<th>Regional distribution</th>
<th>Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>2</td>
<td>8.3</td>
<td>1 region</td>
<td>8</td>
</tr>
<tr>
<td>Face</td>
<td>1</td>
<td>4.2</td>
<td>2 regions</td>
<td>2</td>
</tr>
<tr>
<td>Spine</td>
<td>9</td>
<td>37.5</td>
<td>4 regions</td>
<td>4</td>
</tr>
<tr>
<td>Ribs</td>
<td>9</td>
<td>37.5</td>
<td>4 regions</td>
<td>4</td>
</tr>
<tr>
<td>Scapula</td>
<td>6</td>
<td>25</td>
<td>5 regions</td>
<td>3</td>
</tr>
<tr>
<td>Sternum</td>
<td>5</td>
<td>20.8</td>
<td>6 regions</td>
<td>1</td>
</tr>
<tr>
<td>Upper limb</td>
<td>3</td>
<td>12.5</td>
<td>7 regions</td>
<td>1</td>
</tr>
<tr>
<td>Pelvis</td>
<td>9</td>
<td>37.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb</td>
<td>10</td>
<td>41.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The range of serum CA15-3 in total patients was 16.5-41.3 U mL⁻¹, with average of 24.08±5.30 U mL⁻¹. These measures were 26.37±4.74 (20-41) for Group Y and 19.09±1.59 (16.5-22.5) for Group N. The average level of CA15-3 was significantly more in Group Y than Group N (p<0.001).

Of all patients, 32 (91.4%) had normal and 3 (8.6%) had abnormal (elevated) serum CA15-3 level. In metastatic patients (Group Y, n = 24), 21 (87.5%) had normal and 3 (12.5%) had abnormal (elevated) serum CA15-3 level. These Values for non-metastatic patients (Group N, n = 11) were 11 (100%) and 0 (0%), respectively. However, the difference between the groups were not significant (p = 0.536).

Analysis showed that the relation between serum CA15-3 level and area of bone involvement (number of involved bones) was not statistically significant (p = 0.769, rho = -0.063).

Hosmer and Lemershow test showed that use of serum CA15-3 level for evaluation of bone metastasis was suitable (p = 0.999).

We used ROC diagram for anticipation of presence of bone metastasis of breast cancer. With under curve area of 0.964 and p<0.001 (95%CI: 0.91-1.02), this variable is sufficient for this purpose.

We used also table of coordinates of the curve for determination of new cut-off for anticipation of presence of bone metastasis, which revealed the best cut-off of 21.8 U mL⁻¹ for this purpose. The sensitivity and specificity in this cut-off were 91.7 and 91%.

In new cut-off, 12 (34.3%) had normal and 23 (65.7%) had abnormal (elevated) serum CA15-3 level. In metastatic
patients (Group Y, n = 24), 22 (91.7%) had normal and 2 (8.3%) had abnormal (elevated) serum CA15-3 level. These values for non-metastatic patients (Group N, n = 11) were 10 (90.9%) and 1 (9.1%), respectively. The number of cases with abnormal CA15-3 was significantly more in Group Y than Group N (p<0.001, OR = 110, 95% CI: 8.90-1359.17).

**DISCUSSION**

The detection of bone metastasis accurately reflects the prognosis and early detection in the asymptomatic case may alert the clinician to the possible complications inherent in skeletal destruction. Preventive measures may be taken to avert or decrease the related morbidity and mortality (O'Brien et al., 1992). Radiosotope bone scintigraphy is the most sensitive and the most common method for screening bony metastatic disease (O'Brien et al., 1992). In the present study, the results of bone scan and signs of bone involvement were considered as gold standard of diagnosis.

In agreement with this study, Nicolini et al. (1999, 2003) showed that in breast cancer patients the CA15-3 tumor marker panel has a high value in selecting patients with bone metastasis, or at high risk of developing clinically-evident bone metastasis, among the large number of subjects with equivocal bone scan. The study of Estrada-Sánchez et al. (2003) on 100 women with breast cancer showed that the mean value of CA15-3 for the patients without metastatic disease is 16.18 U mL⁻¹ and for patients with bone metastasis is 164.02 U mL⁻¹. This study also, is compatible with our findings although, the CA15-3 level in their study very high. However, this high difference may be due the fact that all of their patients were in stages III or IV.

The early cut-off in our study was CA15-3>30 U mL⁻¹, which did not show any significant difference between two groups as elevated levels. However, in new cut-off of CA15-3>21.8 U mL⁻¹, the elevated levels of CA15-3 was significantly more in patients with bone metastasis (sensitivity of 91.7% and specificity of 91%). Gion et al. (2001) suggested that determination of new cut-off value for CA15-3 for prediction of bone metastasis is of great importance. Indeed, the cut-off values for CA15-3 for the best prediction of distant metastasis including bone metastasis, are different in these patients: CA15-3>30 (Tomlinson et al., 1995; Wojtacki et al., 2001), CA15-3>40 (Ruibal et al., 2006), CA15-3>25 (Buffaz et al., 1999), CA15-3>35 (Estrada-Sánchez et al., 2003), CA15-3>38 (Giai et al., 1996), CA15-3>32 (Duncan et al., 1991) and CA15-3>10 (Gion et al., 2002). This high range of diversity may cause from some reasons including sample size (Petrie and Sabin, 2009) so, that increasing sample size results in more accurate findings. However, the laboratory method used for measurement of CA15-3, is another element that can cause different accuracies and different results. We used ECLI A method.

Tomlinson et al. (1995) showed that all patients with a positive bone scan and raised levels of CA15-3 were subsequently confirmed as having bony metastasis; no patient with normal bone scan and normal CA15-3 developed M+ disease. CA15-3 levels were raised in 83% of patients who developed non-bony distant metastasis.

Wojtacki et al. (2001) assayed CA15-3 concentrations immuno-enzymatically in 333 women with breast carcinoma. In patients with distant metastasis, mean serum CA15-3 values and the percentage of positive results were significantly higher as compared to cases with locoregional relapse and carcinoma of the contralateral breast and those without clinical evidence of relapse. The highest CA15-3 values were observed in patients with liver and multiple metastasis. The CA15-3 sensitivity rates were higher in patients with bone metastasis (91.4%). The study confirmed the validity of serial CA15-3 assays in the early diagnosis of breast metastatic disease (Wojtacki et al., 2001).

O’Brien et al. (1992) evaluated 218 patients with breast cancer over a 4-year period. Of these patients, 33 with metastatic breast carcinoma had an elevated tumor marker level at the time of diagnosis of their metastasis, bone metastasis alone (88%), soft tissue metastasis alone (33%), simultaneous bone and soft tissue metastasis (70%). All metastatic breast disease patients demonstrated elevated marker levels, in agreement with previous studies (Nicolini et al., 2000, 2006; Arslan et al., 2000; Giovanella et al., 2002; O’Hanlon et al., 1995; Hou et al., 1995, 1999). They recommend CA15-3 as a simple, reliable and inexpensive screening method for detecting bone metastasis in the patient with breast carcinoma (O’Brien et al., 1992). Inversely, Giai et al. (1996) showed the elevated levels of CA 15.3 were mainly related to visceral metastasis. Gion et al. (1991) concluded from the present findings that CA15.3 in primary untreated breast cancer is a marker of tumor burden as well as of the tendency of local invasiveness.

Yıldız et al. (2004) concluded that although serial tumor marker measurements are an efficient and cost effective method of monitoring disease progression, it does not allow prediction of the bone scan results; so it is not justifiable to reject a bone scan on the basis of these markers.

In agreement with Giai et al. (1996), this study revealed no significant relation between serum CA15-3 concentrations and multifocality or regional involvement.
of bone metastasis. However, other studies have demonstrated higher sensitivity of the CA15-3 test in detecting multiple bone metastasis (Wojtacki et al., 2001; Duncan et al., 1991) although, the group of patients was too small to make our observation conclusive.

However, the confounding factors have been considered in this issue: CA15-3 level has been related with tumor size (Rui et al., 2006; Martin et al., 2006) as well as primary untreated tumor (Gion et al., 1991) and biological characteristics of tumor such as estrogen or progesterone receptor status (Nishimura et al., 2003) although, showed that Duncan et al. (1991) there was no association between the CA15.3 concentration and the apparent tumor load. The anatomical type of bone has no any effect on serum tumor marker concentration between patients with normal and elevated levels of tumor markers in metastatic patients (Gedik et al., 2006). Also, Gion et al. (1991) found no relationships between serum CA15-3 and receptor status, but CA15-3 was significantly higher in medullary than in ductal carcinoma (Gion et al., 1991). Gion et al. (2001) in another study, showed that the time of CA15-3 measurement during the follow-up period is effective on the achieved results. In patients with metastatic disease and normal CA 15-3, the tumor marker will increase gradually (Estrada-Sánchez et al., 2003).

Younsi et al. (1997) in a retrospective study of the clinical records of 158 women followed for breast cancer, showed that those patients with normal CA 15-3 levels and positive bone scans showed a subsequent rise in CA 15-3 levels which frequently became elevated with a average delay of 15 months.

CA15-3 tumor marker panel can be used as a preliminary screen to select patients who need further radiological investigation, thus, confirming its important role in the postoperative follow-up of breast cancer patients. However, the use of this tumor marker alone in decision making and clinical management is not recommended (Gedik et al., 2006; Estrada-Sánchez et al., 2003; Tomlinson et al., 1995; Wojtacki et al., 2001; Nicolini et al., 2006; Yildiz et al., 2004). The CA15-3 might be assayed alongside a bone scan to confirm positive or negative results. Another role might be screening for breast cancer metastasis in departments with limited access to bone scans and other imaging facilities. The CA15-3 might also be used in monitoring for the development of distant metastasis during follow-up. It is, however, unlikely that CA15-3 can substitute directly for a bone scan or other imaging currently used routinely by clinicians (Tomlinson et al., 1995). The early detection of recurrent foci may be accomplished using such highly sensitive tumor marker together with modern imaging technologies (Uchida et al., 2008).

On the basis of the present results, before considering CA15-3 for clinical decision-making, further studies should be performed on other independent case series to confirm the observed prognostic relationships. Clinical trials are now necessary to determine the effect of using tumor markers such as CA15-3 on patient morbidity and mortality.

CONCLUSION

In conclusion, CA15-3 tumor marker panel can be used as a preliminary screen to select patients who need further radiological investigation, thus, confirming its important role in the postoperative follow-up of breast cancer patients. This study showed that the serum level of CA 15-3 antigen is higher in the patients with bone metastatic breast cancer; however, the recommended cut-off point might not be suitable for Iranian patients. Further studies with large sample sizes are recommended.

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