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Tumour Marker CA15-3: Possible Uses in the Routine Management of Breast Cancer

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Tumour markers are a potentially powerful means of obtaining information about cancers whilst causing minimal morbidity, inconvenience and cost. CA15-3 has been suggested as a marker of distant metastasis (M+ disease) in breast cancer. We have measured CA15-3 in 77 patients with carcinoma of the breast in order to determine whether routine assay of this tumour marker would be useful in the oncology unit of a district general hospital. A highly significant correlation existed between elevated CA15-3 levels (≥ 30 U/ml) and M+ disease. The CA15-3 assay was found to have a sensitivity of 70%, a specificity of 96% and a predictive value of 87%, in agreement with previous studies. There was evidence that CA15-3 levels frequently increased in advance of otherwise detectable distant metastases. 70 patients had a 99m Tc bone scan close to the date on which CA15-3 was measured. All patients with a positive bone scan and raised levels of CA15-3 were subsequently confirmed as having bony metastases; no patient with normal bone scan and normal CA15-3 developed M+ disease (to the date of follow-up). CA15-3 levels were raised in 83% of patients who developed non-bony distant metastases. In clinical practice it may be possible to exploit the high specificity of CA15-3, in order to provide additional information to that already determined by current investigations. For example, CA15-3 might be assayed alongside a bone scan to confirm positive or negative results. Another role might be as a screen for breast cancer metastases in departments with limited access to bone scans and other imaging facilities. CA15-3 might also be used in monitoring patients for the development of distant metastases during follow-up. It is, however, unlikely that CA15-3 can susbtitute directly for a bone scan or other imaging currently used routinely by a department. Clinical trials are now necessary to determine the effect of using tumour markers such as CA15-3 on patient morbidity and mortality.

Key words: breast cancer, distant metastases, tumour marker CA15-3, bone scan
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INTRODUCTION

SERUM TUMOUR markers can help in the diagnosis and management of malignant disease, if they are sensitive, specific and cheap to assay [1, 2]. CA15-3 has been proposed as an indicator of distant metastasis (M+ disease) in breast carcinoma [3–5], and measures milk mucin secreted by the tumour. This mucopolysaccharide is quantified using serum or plasma by immunoradiometric means [3, 4]. In general, the following conclusions may be drawn from other studies [3, 6–17], although results are inconsistent: (a) in normal individuals, CA15-3 levels vary from 0 to about 30 U/ml; values of 30 or more are raised; (b) some non-breast malignancies and other diseases, such as renal or hepatic failure, can cause CA15-3 to be elevated; (c) levels of CA15-3 depend on tumour mass; (d) CA15-3 is insufficiently sensitive in detecting primary or local (N+) disease and cannot be used routinely for screening, diagnosis or follow-up of such cancers; (e) there is an association between detectable M+ disease and elevated CA15-3, with a specificity approaching 100% with respect to normal individuals and benign breast disease; for M0 disease, the sensitivity is 30–50%, rising to 75–90% for M+ disease; (f) some studies have shown that CA15-3 levels rise in approximately 50% of patients prior to the development of detectable M+ disease; (g) CA15-3 appears not to vary with the site of distant metastases; (h) the concurrent use of CA15-3 and other tumour markers may improve sensitivity (at the expense of specificity); and (i) it is unclear whether or not the use of CA15-3 alters patient prognosis.

The purpose of this study was to determine worthwhile ways of using CA15-3 in clinical practice. We particularly investigated whether CA15-3 levels are associated with distant metastasis of breast tumours (and hence with prognosis and management); and whether these data agree with those of other workers. We also examined whether CA15-3 levels rise before recurrent

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disease is detectable, and the potential for following patients through treatment or whilst in apparent remission by monitoring CA15-3. A comparison of CA15-3 with bone scans and other imaging in detecting disease was made, and the potential for CA15-3 to replace any investigations or alter management was examined, as was the question of whether CA15-3 should be measured routinely or in selected patients.

PATIENTS AND METHODS

CA15-3 was measured in all patients booked for a 99m Tc bone scan at the Berkshire Oncology Unit (Royal Berkshire Hospital, Reading, U.K.) between 3 November 1988 and 8 November 1990. 57 patients were new referrals from General Surgery, and in all these cases, CA15-3 assays were performed 0–6 months after initial presentation. In 20 further cases, a bone scan was booked because there was clinical suspicion of recurrent disease; CA15-3 was, therefore, measured between 1 and 10 years after these patients first presented. In all 77 cases, the CA15-3 assay was performed according to the manufacturers' protocol [3, 4].

It was intended that CA15-3 be studied in parallel with and as a potential alternative to the 99m Tc bone scan. However, only 70 of the 77 cases actually proceeded to the scan. Of the 7 cases not imaged by bone scan, 1 died before the scan could be performed and 6 patients decided against the scan in the absence of bone symptoms (without knowing their CA15-3 result). Isotopic labelling for bone scans was performed using the Medronate II Technetium Agent Kit (Amersham, U.K.), with a labelling efficiency approaching 100%. Other technical procedures followed standard protocols. The results of bone scan radiographs were reported independently and according to standard departmental procedure by the Departments of Radiology & Medical Physics, Royal Berkshire Hospital.

Additional appropriate imaging and other methods were used to search for both bony and non-bony metastases (and the results of these were also compared with contemporaneous CA15-3 levels). Techniques used depended on clinical judgement and patient wishes, but included routine biochemical tests, plain X-radiographs, CT or ultrasound scans and biopsy with histology or cytology. Standard clinical and biochemical markers of metastasis (for example, Ca^{2+}, serum alkaline phosphatase and liver function tests) were used to provide suspicion of metastatic disease, but were not used as definitive indicators of secondary spread, and details are not given here.

Patients' tumours were grouped according to the TNM classification [18] using the combined results of clinical findings, biochemical tests, imaging and histopathological assessment. CA15-3 levels were not used in assessing patients' TNM classifications. Similarly, a single, uncorroborated bone scan was not taken as sufficient evidence to provide TNM status.

Follow-up information was available for a mean time of 50 months after presentation (range 18 months–15 years). Other data collected included patient age, menstrual status, date of detection of local or distant metastases and the use of chemotherapy. It was not possible to follow the rise and fall of CA15-3 levels during response to treatment or after relapse.

Standard analytical methods and statistical tests of association (in practice, χ^2 tests) were used to calculate the specificity, sensitivity and predictive value of the CA15-3 assay and to compare it with bone scans and other imaging.

RESULTS

At presentation, 42 of the 77 patients had disease localised to the breast on histopathological grounds, 12 patients were clinically axillary-node-negative, 23 patients had node-positive disease on histopathological grounds and no patient had known distant metastases (Table 1).

Table 1. TNM status of patients at presentation

TNM stage	No. of patients (%)
N0M0 (clinically)	12 (16)
N0M0 (histologically)	42 (55)
N + M0 (histologically)	23 (30)
M+	0 (0)
Total	77

Table 2. Association between raised CA15-3 and distant metastases by end of follow-up

	No. patients with proven M+ disease	No. patients without proven M+ disease	Total
Raised CA15-3	13	2	15
Normal CA15-3 (< 30 U/ml)	5	57	62
Total	18	59	77

$\chi^2 = 39.1$, Yates' correction, d.f. = 1; $P < 0.001$.

To the date of follow-up, 18 individuals (23%) were known to have developed M+ disease. 5 of these 18 patients received chemotherapy. 2 premenopausal patients received adjuvant chemotherapy (details available from authors).

A highly significant correlation was found between elevated CA15-3 levels (≥ 30 units/ml) and M+ disease (Table 2). The CA15-3 assay was found to have a sensitivity of 70%, a specificity of 96% and a predictive value of 87% (all in agreement with previous studies). Numbers of false positives and false negatives are shown in Table 2. All 8 patients with CA15-3 levels above 50 U/ml developed M+ disease.

There was evidence that CA15-3 levels rose in advance of otherwise detectable distant metastases. Of the 18 cases who developed M+ disease during follow-up, 5 had CA15-3 levels measured 3–24 months before distant metastases were detected by the usual methods. Of these 5, 4 (80%) had elevated CA15-3 while the other patient had normal CA15-3 15 months before M+ disease was discovered. 2 patients with raised CA15-3 did not develop M+ disease during the period of follow-up (approximately 48 months in each of these cases).

Table 3. CA15-3 levels in patients with M+ disease

Total developing M+ disease (18)			
CA15-3 measured within 1 month of discovery of M+ disease (13)		CA15-3 measured 3 to 24 months before discovery of M+ disease (5)	
Raised CA15-3	Normal CA15-3	Raised CA15-3	Normal CA15-3
9 (69%)	4 (31%)	4 (80%)	1 (20%)

Table 4 compares CA15-3 with the contemporaneous bone scan and with other appropriate imaging of those patients who had suspected non-bony distant metastases. Considering bony metastases first, it is notable that all patients with a positive bone scan and raised CA15-3 were subsequently confirmed as having bony metastases. Moreover, no patient with normal bone scan and normal CA15-3 developed M+ disease over the period of follow-up. Bone scan sensitivity was 92%, specificity was 88% and predictive value was 58%. Numbers of false positives and false negatives are shown in Table 4. The 1 patient with a false negative bone scan was shown to have osteolytic bony metastases on plain X-radiographs. By comparison with CA15-3, the bone scan produced more false positives and fewer false negatives. There was, however, a non-significant difference between the bone scan and CA15-3 in detecting bony metastases ($\chi^2 = 2.60$, Yates' correction, d.f. = 1, $P > 0.10$) in the sample studied here.

6 patients developed non-bony distant metastases by the time of follow-up. Of these, 3 had spread to the brain (confirmed on CT scan), 2 had lung metastases (shown on chest X-radiograph and CT scan) and 1 had liver metastases with malignant ascites (confirmed on ultrasound scan and ascitic tap). The imaging used produced no known false positive or false negative cases. CA15-3 levels were raised in 5 of the 6 patients (83%) with non-bony metastases.

DISCUSSION

CA15-3 is a marker of distant metastasis in breast carcinoma with high specificity and moderate sensitivity. In some patients with M+ disease, CA15-3 levels may be raised before metastases can be detected by other means. Patients whose bone scan and CA15-3 results are concordant may be told with confidence whether or not they have bony metastases. CA15-3 levels are also raised in the great majority of patients with non-bony M+ breast cancer.

At the time of study, each CA15-3 assay was costed in the U.K. at £17.50 (compared with approximately £50 for a bone scan). The potential uses of CA15-3 in clinical practice fall into two main categories: improved or more accurate diagnosis and increased convenience or cost-effectiveness. CA15-3 might be used in diagnosis by improving the diagnostic accuracy of bone scans, monitoring patients in follow-up and detecting metastases early. CA15-3 might be a cheap or easy way of screening for M+ breast cancer and avoiding expensive or inconvenient imaging.

The actual use to which CA15-3 would be put depends on the clinical practice and financial resources of the oncology department. In general, those uses which exploit the high specificity of CA15-3 will be the most likely. These uses will probably provide additional information to that already known. Attempts to substitute CA15-3 for other investigations are likely to be less successful, owing to its only moderate sensitivity (that is, the number of false negatives will be too great to be tolerated). It follows that employing CA15-3 is more likely to lead to extra expense than to save money.

Three specific uses must be considered. The first, as stated above, would be as an adjunct to a bone scan, in order to provide confirmation of positive or negative results. Those patients with discordant bone scans and CA15-3 levels would have to be investigated further with, for example, a repeat bone scan, further CA15-3 measurements and closer follow-up.

The second possible use of CA15-3 is to measure levels in all (or selected) breast cancer patients as a screen for M+ disease. An analogy is the use of prostate-specific antigen in prostatic enlargement. In those patients with raised CA15-3, further investigations would be performed to confirm, localise and treat metastases. Departments most likely to use CA15-3 in this way would not currently perform imaging such as bone scans as a routine investigation in all patients presenting with breast cancer (see below).

A third possible role for CA15-3 lies in monitoring patients in follow-up. Whilst the use of CA15-3 for, say, monitoring response to therapy for M+ disease has not been considered here, the results of this study suggest a use for CA15-3 whilst following-up patients known to have M0 disease only. A rise in CA15-3 to abnormal levels would be highly suggestive of the development of distant metastases (even if other investigations were negative).

All the above uses for CA15-3 will require additional resources. Despite the problems with its lack of sensitivity, might CA15-3 actually save money in some cases? The most obvious such role is a direct substitution for a bone scan. However, the difference between CA15-3 and bone scans in this study (Table 4) approaches significance and cannot, in itself,

Table 4. Comparison between elevated CA15-3 and a contemporaneous bone scan or other appropriate imaging

CA15-3	Bone scan	Proven bony metastases	Proven non-bony metastases	Metastases not proven	Total
+	+	7	0	0	7
+	−	1	5	2	8
−	+	4	1	7	12
−	−	0	0	43	43
Total		12	6	52	70

The table shows numbers of patients categorised according to raised (+) or normal (−) CA15-3 levels; bone scans reported as 'possible', 'suspicious of', or 'suggestive of' metastases (or equivalent wording) (+) or reported as 'normal' or probable non-malignant disease (−); and the presence of proven bony or non-bony distant metastases, or distant metastases not proven.

provide conclusive evidence that CA15-3 could replace bone scans. There are two main reasons for this: first, the problems of false negatives that exist with CA15-3 will outweigh those of false positives that exist with bone scans (see above) and second, CA15-3 cannot localise bony metastases.

However, could CA15-3 be used to select out patients who are most likely to have true positive bone scans, thereby reducing the number of bone scans, saving money and reducing morbidity? This way of using CA15-3 would save about £30 per patient in U.K. departments that currently perform bone scans on all patients presenting with breast cancer. If this strategy had been followed here, 70 patients would have had CA15-3 assayed. Of these, 55 had normal CA15-3 and would have been spared a bone scan. However, 4 of these 55 patients did have bony metastases, despite their normal CA15-3. Using CA15-3 in this way would have provided false reassurance to these patients and have caused delays in treatment. In our view, these data do not provide clinical justification for using CA15-3 to select patients for bone scans, outweighing any financial arguments for using CA15-3 in this way.

This study illustrates the potential uses for tumour markers such as CA15-3 in indicating distant breast cancer metastases. We have shown that, in general, markers like CA15-3 are most promising in areas where they provide extra information, rather than substituting for current investigations. Prospective trials are now necessary to determine the effect of using CA15-3 and related tumour markers on patient morbidity and mortality.

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