Utility of CA 15-3 in diagnosis of Breast Cancer Recurrence. An Observational Study.

Musaab R. Al-Bayati*
MB.Ch.B, FICMS, MRCP, ESMO C.
*Dept. of medical oncology, Alhabobi hospital, Thiqar, Iraq
Email : mousabraji@yahoo.com

Abstract
Background : CA 15-3 is the commonest tumor marker for breast cancer. Elevated serum levels of this marker was shown to be a predictor of disease recurrence in patients with localized breast cancer. This study aimed to determine the sensitivity of serum CA 15-3 level in the detection of breast cancer recurrence in relation to the molecular subtype of breast cancer, type of recurrence and the number and sites of distant metastasis.
Methods : Retrospective observational study of patients with localized breast cancer followed until relapse. Serum level of CA 15-3 at first documentation of relapse was compared between patients in respect to the molecular subtype of breast cancer, type of recurrence and the number and sites of metastasis.
Results : Elevation of CA 15-3 were found in 56% of patients at relapse. Only 6% of patients with locoregional relapse shows elevation of this marker compared with 62% of patients with distant metastasis. Elevation of CA 15-3 were more sensitive for detection of relapse in patients with luminal subtype (62%) than in patients with HER2 enriched (45%) and triple negative (35%) breast cancers. The test was more sensitive in patients with bone (69%), lung (65%) and liver (62%) metastasis than in patients with brain metastasis (25%).
Conclusions : CA 15-3 is a relatively sensitive marker for detection of breast cancer recurrence. However, this sensitivity may be hampered in patients with isolated locoregional relapses and in patients with HER2 enriched and triple negative breast cancers.
Keywords : Breast cancer, Relapse, CA 15-3, Molecular subtypes.

Introduction

Breast cancer comprise several molecular subtypes, which are commonly divided into clinical subtypes based on receptor status, namely the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2-neu (HER2) receptor [1]. About one third of patients with localized breast cancer will eventually develop metastatic disease with a variable disease free interval ranging from few months to decades [2]. CA 15-3 is a mucinous antigen encoded by the MUC1 gene. The function of MUC1 is not completely understood, but it might play a role in cell adhesion facilitating detachment of malignant cells and this will lead to cancer invasion and metastasis [3]. Serum levels of CA15-3, the most commonly used tumor marker for breast cancer, is rarely elevated in patients with localized breast cancer, while the majority of patients with metastatic breast carcinoma have elevated levels [4]. Progressive rise in serum level of CA 15-3 has been shown to be a strong predictor of disease recurrence in patients with localized breast cancer [5, 6]. In addition, elevated CA15-3 in patients with metastatic breast cancer indicate high tumor burden and have major impact on survival [7]. Although the current American Society

of Clinical Oncology guidelines do not recommend the use of circulating CA 15-3 for monitoring patients for recurrence after primary breast cancer therapy [8], measurement of serum levels of CA 15-3 is widely used in clinical practice because it is a rapid, noninvasive, reproducible, and quantitative test [9]. Studies have shown that elevated serum levels of CA 15-3 have a high specificity for detecting relapse of breast cancer [10], but, the sensitivity of the test was variable depending on many factors such as the molecular subtype of breast cancer, the type of recurrence (locoregional or distant), location of the metastasis, and the number of metastatic sites [11, 12, 13]. In this study, patients with localized breast cancer were followed by serial CA15-3 measurements until documentation of relapse. Serum level of CA 15-3 at relapse were correlated with the patients age, molecular subtype of breast cancer, type and location of relapse and the number of metastatic sites.

Patients and Methods

Study design

A retrospective observational study of patients with localized breast cancer who have received treatment at Al-Nasiriyah medical oncology department between 2012 – 2017.

Inclusion and Exclusion Criteria

All enrolled patients in the study must have :

1- Underwent mastectomy or breast conserving surgery with adequate axillary staging.
2- Received adjuvant therapy according to international guidelines.
3- No any evidence of metastatic disease before surgery.
4- Normal baseline serum level of CA 15-3.
5- Results of clinical examination, imaging studies and serum level of CA 15-3 every 3 – 6 months during the study period.

Methods

Serum CA 15-3 levels were determined using Enzyme Linked Fluorescent Assay (ELFA) principle using mini VIDAS system supplied by BioMerieux Inc. The cut-off value of CA 15-3 were 30 U/ml. Levels above 30 U/ml were regarded as elevated and below this level were regarded as normal.

Documentation of recurrence or metastatic disease was made by clinical examination and radiological studies and confirmed by histopathology if clinically indicated.

Data were collected manually by review of the patients files and follow up visits. Serum level of CA 15-3 at the day of confirmation of relapsed disease was regarded as the study end point.

Differences in variables were evaluated by chi-square test. All P-values were two-sided and a P-value of less than 0.05 was considered statistically significant.

Results

From 2012 to 2017, A total of 474 patients with localized breast cancer treated at Al-Nasiriyah oncology deprtment. From this group, 138 patients have developed relapsed disease, and fulfill the inclusion criteria to be enrolled in the study. Table 1 shows the baseline characteristics of the study population.

From the enrolled patients, 78 out of 138 patients were found to have elevated serum CA 15-3 level at the time of relapsed disease, suggesting an overall test sensitivity of 56% in the detection of relapse. However, the sensitivity of the test in patients with isolated locoregional relapse is only

6%, while it is 62% in patients with distant metastasis.

Table 2 shows the sensitivity of the test in different patients groups. The test sensitivity is highest in patients with hormone receptor positive disease (62%), and lowest in patients with triple negative disease (35%). Also, the test have low sensitivity in patients with isolated cerebral metastasis (25%).

Table 3 shows a comparison between patients with elevated and normal CA 15-3 at the time of relapse according to molecular subtype, locoregional or distant metastasis, number and location of metastases. Among these variables, only the molecular subtype of breast cancer and the type of metastasis (locoregional vs distant metastasis) reach statistical significance.

Table 1 Baeline Characteristics of Patients	
Characteristic	No (%)
Overall	138
Age at diagnosis (Years)	
Median = 48 (Range 26 – 85)	
< 35	13 (10)
35 – 50	72 (52)
51 – 65	38 (27)
> 65	15 (11)
Molecular Subtype	
LUMINAL	**101 (73)**
HR positive/HER2 negative	*78 (56)*
HR positive/HER2 positive	*23 (17)*
Non-LUMINAL	**37 (27)**
HR negative/HER2 positive	*20 (14)*
HR negative/HER2 negative	*17 (13)*
Type of Recurrence	
Locoregional	15 (11)
Distant Metastasis	123 (89)
Number of distant metastases (n= 123)	
Single metastasis	97 (79)
Multiple metastases	26 (21)
Sites of single metastasis (n= 97)	
Bone	33 (34)
Lungs and Pleura	23 (24)
Liver	19 (20)
Brain	12 (12)
Omental and Ovaries	9 (9)
Bone marrow	1 (1)

Table 2 Sensitivity of elevated CA 15-3 in detection of relapse according to age, molecular subtype, type of recurrence, number and sites of metastasis		
Characteristic	**Total no.**	**Sensitivity (%)**
Age at diagnosis (Years)		
Age groups		
< 35	13	30
35 – 50	72	61
51 – 65	38	60
> 65	15	46
Molecular Subtype		
LUMINAL	**101**	**62**
HR positive/HER2 negative	*78*	*62*
HR positive/HER2 positive	*23*	*60*
Non-LUMINAL	**37**	**40**
HR negative/HER2 positive	*20*	*45*
HR negative/HER2 negative	*17*	*35*
Type of Recurrence		
Locoregional	15	6
Distant Metastasis	123	62
No. of distant metastases (n=123)		
Single metastasis	97	62
Multiple metastases	26	66
Sites of single metastasis (n=97)		
Bone	33	69
Lungs and Pleura	23	65
Liver	19	63
Brain	12	25
Omental and Ovaries	9	55
Bone marrow	1	N/A

Table 3 Comparison between Patients who have elevated and normal CA 15-3 at relapse				
Characteristic	**Total** *(n = 138)*	**Elevated** *(n = 78)*	**Normal** *(n = 60)*	**P value**
Age at diagnosis (Years)				
Age groups				
< 35	13	4	9	
35 – 50	72	44	28	NS
51 – 65	38	23	15	
> 65	15	7	8	
Molecular Subtype				
LUMINAL	**101**	**63**	**38**	
HR positive/HER2 negative	*78*	*49*	*29*	
HR positive/HER2 positive	*23*	*14*	*9*	< 0.5
Non-LUMINAL	**37**	**15**	**22**	
HR negative/HER2 positive	*20*	*9*	*11*	
HR negative/HER2 negative	*17*	*6*	*11*	
Type of Recurrence				
Locoregional	15	1	14	< 0.5
Distant Metastasis	123	77	46	
No. of distant metastases (n=123)				

Single metastasis	97	58	39	NS
Multiple metastases	26	20	6	
Sites of single metastasis (n=97)				
Bone	33	23	10	
Lungs and Pleura	23	15	8	
Liver	19	12	7	NS
Brain	12	3	9	
Omental and Ovaries	9	5	4	
Bone marrow	1	0	1	

Discussion

In this study which included patients with early breast cancer followed until clinical relapse, the overall sensitivity of CA 15-3 in the detection of relapse was 56% . In two studies by Pedersen et al and Stieber et al, the sensitivity of elevated CA 15-3 in the detection of relapse was 49.4% and 55.6% respectively [13, 14].

In their report on the recommendations for the use of serum tumor markers in breast cancer, The National Federation of French Cancer Centres states that the sensitivity of tumor markers in the diagnosis of local recurrence is poor, but their usefulness (particularly that of CA 15.3) in the early diagnosis of breast cancer metastases is clear [15]. A recent study by Riedinger et al, confirms that elevated CA 15-3 is a sensitive marker for the early detection of distant metastasis, but, not for locoregional recurrence [16]. The results in this study of very low sensitivity of CA 15-3 in detection of locoregional recurrence (6%) compared with distant metastasis (62%) confirms these findings.

Recent studies have shown that elevated levels of serum CA 15-3 are strongly associated with the molecular subtype of breast cancer, and patients with luminal breast cancer are more likely to have elevated CA 15-3 at relapse than patients with HER2 enriched and basal like breast cancers [17, 18]. Since CA 15-3 is a mucinous antigen, it is thought that it is overexpressed by luminal subtype of breast cancer more frequently than in the less differentiated subtypes, namely, HER2 enriched and triple negative -basal like subtype [19]. In the present study, the molecular subtype of breast cancer was significantly associated with elevation of CA 15-3 at relapse (p value < 0.05).

Previously published studies have shown that the highest proportions of elevated CA 15-3 were found in patients with bone, liver and lung metastasis [20, 21]. Results in this study agrees with these findings, in addition, a low percentage of patients (25%) with isolated brain metastasis exhibit elevation in CA 15-3 which needs further studies to confirm these results.

Although several studies have shown that patient with multiple metastatic sites are more likely to exhibit elevation in CA 15-3 than patients with single metastasis [7, 22], this study did not found a significant difference in CA 15-3 elevation between patients with single or multiple metastasis which may be explained by inadequate evaluation to detect metastatic sites at time of relapse in some patients.

Conclusions

In this observational study, CA 15-3 seems to be a relatively sensitive marker for the detection of recurrence of breast cancer, especially in patients with luminal breast cancer. The overall sensitivity of the test was 56%. If we exclude patients with locoregional recurrence, the test sensitivity increase to 62% in patients with distant metastatic disease. However, the test

sensitivity is low in patients with triple negative (35%) and HER2 enriched (54%) breast cancers necessitating the use of other markers for the diagnosis of recurrence.

References

1- Santa-Maria CA, Gradishar WJ. Changing Treatment Paradigms in Metastatic Breast Cancer: Lessons Learned. JAMA Oncol 2015 Jul;1(4):528-34.
2- Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. Breast 2017 Feb;31:46-50.
3- Quaranta M, Daniele A, Coviello M et al. MMP-2, MMP-9, VEGF and CA 15.3 in breast cancer. Anticancer Res 2007 Sep-Oct;27(5B):3593-600.
4- Chu WG, Ryu DW. Clinical significance of serum CA15-3 as a prognostic parameter during follow-up periods in patients with breast cancer. Ann Surg Treat Res 2016 Feb;90(2):57-63.
5- Keshaviah A, Dellapasqua S, Rotmensz N et al. CA15-3 and alkaline phosphatase as predictors for breast cancer recurrence: a combined analysis of seven International Breast Cancer Study Group trials. Ann Oncol 2007 Apr;18(4):701-8.
6- Molina R, Barak V, van Dalen A et al. Tumor markers in breast cancer- European Group on Tumor Markers recommendations. Tumour Biol 2005 Nov-Dec;26(6):281-93.
7- Lee JS, Park S, Park JM et al. Elevated levels of serum tumor markers CA 15-3 and CEA are prognostic factors for diagnosis of metastatic breast cancers. Breast Cancer Res Treat. 2013 Oct;141(3):477-84.
8- Harris L, Fritsche H, Mennel R et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007 Nov 20;25(33):5287-312.
9- Park BW, Oh JW, Kim JH et al. Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes. Ann Oncol 2008 Apr;19(4):675-81.
10- Vizcarra E, Lluch A, Cibrian R et al. Value of CA 15.3 in breast cancer and comparison with CEA and TPA: a study of specificity in disease-free follow-up patients and sensitivity in patients at diagnosis of the first metastasis. Breast cancer Res Treat 1996;37(3):209-16.
11- Konan S, Goussot V, Desmoulins I et al. Clinical value of CA 15-3 for early detection of relapse in locally advanced breast cancer. Bull Cancer 2015 Oct;102(10):834-44.
12- Wu SG, He ZY, Zhou J et al. Serum levels of CEA and CA15-3 in different molecular subtypes and prognostic value in Chinese breast cancer. Breast 2014; 23:88–93.
13- Pedersen AC, Sorensen PD, Jacobsen EH et al. Sensitivity of CA 15-3, CEA and serum HER2 in the early detection of recurrence of breast cancer. Clin Chem Lab Med 2013; 51:1511–1519.
14- Stieber P, Nagel D, Blankenburg I et al. Diagnostic

efficacy of CA 15-3 and CEA in the early detection of metastatic breast cancer-A retrospective analysis of kinetics on 743 breast cancer patients.

15- Basuyau JP, Blanc-Vincent MP, Bidart JM et al. Summary report of the Standards, Options and Recommendations for the use of serum tumour markers in breast cancer: 2000. Br J Cancer. 2003 Aug;89 Suppl 1:S32-4.

16- Riedinger JM, Goussot V, Desmoulins I et al. CEA and early detection of relapse in breast cancer subtypes: Comparison with CA 15-3. Bull Cancer. 2016 May;103(5):434-43.

17- Yerushalmi R, Tyldesley S, Kennecke H et al. Tumor markers in metastatic breast cancer subtypes: frequency of elevation and correlation with outcome. Ann Oncol. 2012 Feb;23(2):338-45.

18- Geng B, Liang MM, Ye XB et al. Association of CA 15-3 and CEA with clinicopathological parameters in patients with metastatic breast cancer. Mol Clin Oncol. 2015 Jan;3(1):232-236.

19- Lim E, Vaillant F, Wu D et al. Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers. Nat Med 15: 907-913, 2009.

20- al-Jarallah MA, Behbehani AE, el-Nass SA et al. Serum CA-15.3 and CEA patterns in postsurgical follow-up, and in monitoring clinical course of metastatic cancer in patients with breast carcinoma. Eur J Surg Oncol. 1993 Feb;19(1):74-9.

21- Tampellini M, Berruti A, Gorzegno G et al. Independent factors predict supranormal CA 15-3 serum levels in advanced breast cancer patients at first disease relapse. Tumour Biol. 2001 Nov-Dec;22(6):367-73.

22- Bidard FC, Hajage D, Bachelot T et al. Assessment of circulating tumor cells and serum markers for progression-free survival prediction in metastatic breast cancer: a prospective observational study. Breast Cancer Res. 2012 Feb 13;14(1):R29.