Cancer Imaging (2006) **6,** 4–6
DOI: 10.1102/1470-7330.2006.0001

CI

e-med
www.e-med.org.uk

ARTICLE

Contrast enhanced ultrasound of breast cancer

E Cassano*, S Rizzo*, A Bozzini*, S Menna* and M Bellomi†

**Breast Imaging Unit, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy; †Department of Radiology, European Institute of Oncology - School of Medicine, University of Milan, Milan, Italy*

Corresponding address: Enrico Cassano, Breast Imaging Unit, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy. E-mail: enrico.cassano@ieo.it

Date accepted for publication 21 November 2005

Abstract

The importance of ultrasound examination in the diagnosis of breast cancer has been widely demonstrated. During the last few years, the introduction of ultrasound contrast media has been considered a promising tool for studying the vascular pattern of focal lesions within the breast. Our purpose was to assess whether contrast-enhanced (CE) ultrasound examination, performed using specific contrast imaging modes, can be helpful for detection and characterization of breast lesions, and for prediction of the response of breast cancer to therapy.

Keywords: *Breast cancer; ultrasound; contrast medium.*

The second generation of ultrasound contrast media (Sonovue) is a preparation of stabilized microbubbles of sulphur hexafluoride, a poorly soluble and innocuous gas, with no protein-based materials, for use as a contrast medium for B-mode or Doppler ultrasound. These stable microbubbles which are resistant to pressure and are isotonic in human plasma, are less viscous than blood[1,2]. Sonovue does not diffuse into the extravessel compartment, remaining within the blood vessels (blood-pool agent) until the gas dissolves and it is then eliminated in expired air. Previous data have shown that Sonovue can be helpful in demonstrating the macro- and microcirculation of hepatic lesions. Therefore, in January 2004 we started a pilot study to evaluate if the use of contrast-enhanced (CE) ultrasound can assess the microcirculation characteristics of four different types of breast lesions less than or equal to 2 cm in 50 patients: 15 fibroadenomas, 15 lesions classified at cytology as probably malignant (C4), 10 lesions with microcalcifications and 10 post-operative scars with suspected recurrence. The models used for defining the microcirculation were: qualitative distribution of contrast medium using semi-quantitative scales, and intensity/time curves within the lesion during contrast administration. CE ultrasound exam was performed on a Technos Esaote machine, using 8–10 MHz probes, specific software CnTi, 2nd harmonica, gain was 125, power 16 kPa instead of 1 kPa, targeting the inferior margin of the lesion.

The results were then compared to the histological specimens obtained either by surgery or by biopsy, and, only for patients with suspected recurrence on the scar, and also to the intensity/time curves obtained with a contrast-enhanced MR. The results of the first part of the study were negative, indicating no significant differences among the four groups concerning the microcirculation characteristics detected by CE ultrasound[3–5].

After this study, another 15 patients with a breast cancer lesion 1–2.5 cm in diameter were enrolled. All 15 patients underwent mammography, basal ultrasound, and CE ultrasound, before undergoing surgery, in order to study the appearance of the microcirculation of these lesions and to compare these data with the surgical specimens. The results of this study demonstrated inhomogeneous contrast enhancement curves making it impossible to standardize the curves, so that no further patients were enrolled. Since the previous studies did not show any significant advantage using the current settings of CE ultrasound to differentiate the microcirculation characteristics of different breast cancer

lesions, in January 2005 a new setting was installed on the ultrasound machine based on the indications from a new European research cooperative group, PUMEB (Perfusion Ultra Sound Multicenter European Breast Study). Hence, according to the different topics identified in the first meeting of the PUMEB group, we started a new pilot study designed to assess the biological effects of neoadjuvant therapy performed with monoclonal antibody c-erb-B2 (Trastuzumab) which has recently been approved for treatment of breast cancer patients who show an over-expression of HER2/neu, but its mechanism is still unclear. Preliminary results on its use before surgery have shown a volumetric reduction of lesions in 54.5% of treated patients, likely due to immuno-modulated cell cytotoxicity.

In this pilot study, six patients with breast cancer lesions larger than 1 cm, candidates for neoadjuvant therapy with Trastuzumab for 4 weeks (because they showed an over-expression of HER2/neu), were selected to undergo two CE ultrasound exams, one before starting and one following the end of Trastuzumab therapy. The aim of this study was to visualize the distribution of the microcirculation[6] and its changes after dimensional reduction induced by Trastuzumab, in order to assess if the microcirculation characteristics of a breast cancer can predict the response to therapy with Trastuzumab. Inclusion criteria for patients were: histological diagnosis of breast cancer suitable for surgery, the expression of C-erbB2 2+/Fish+ and c-erb B2 3+, age range 18–75 years-old, performance status 0–2 (according to the ECOG scale), no psychiatric pathologies, personal signature on a dedicated informed consent form stating explicit desire of the patient to complete the whole follow-up. Exclusion criteria included: patients undergoing neoadjuvant chemotherapy other than Trastuzumab, previously diagnosed cancers other than breast cancer, cardiopathy, metabolic diseases, neurological diseases, pregnancy, and current infections. The CE ultrasound exam was performed according to the above-mentioned parameters (Technos Esaote machine, 8–10 MHz probes, software CnTi, 2nd Harmonica, 125 gain, power 16 kPa, target to the inferior margin of the lesion) after administration of two contrast medium vials (4.8 ml MDC + 5 ml of saline), with a gap time of 5 min. After the first injection (4.8 ml diluted in 5 ml of saline) the microcirculation of the lesion was studied by recording with clip function for 15 s. After the second injection the dynamic curve of the most contrast-enhanced area was obtained and studied.

The efficacy of Trastuzumab was evaluated by looking at the volumetric reduction of the tumour. The efficacy of tolerability was evaluated by looking at the collateral effects. The sequential steps of the study procedure included: selection of the patient according to the above-mentioned criteria, histological proof of the biological characteristics of the tumour, staging of disease, signing of the specific informed consent form, mammography, CE ultrasound, MR mammography (where possible), administration of Trastuzumab for 4 weeks, clinical and instrumental evaluation of response indices (mammography, CE ultrasound, MR mammography where possible), and surgery. The mechanism of the drug was studied on the surgical specimen. Among the six patients enrolled (mean age 51, age range 38–72), five had invasive ductal cancer (four without central necrosis, one with a wide central necrosis), and one had invasive lobular cancer.

CE ultrasound showed a mean maximum antero-posterior and transverse diameter of lesions pre-therapy of about 15.2 (range 12–18) and 29.5 mm (range 21–42), respectively. The same diameters post-therapy were 12.5 (range 8–17) and 23.5 mm (range 15–36), respectively. Blood flow was indicated as macrocirculation (more than 200 μm) in one case (before and after therapy). Microcirculation was identified in five cases and indicated as patchy microcirculation and diffused microcirculation in three and two cases pre-therapy, and in four and one case post-therapy, respectively.

Qualitative evaluation of CE ultrasound showed that invasive ductal cancers without central necrosis had a wide microcirculation before therapy, and a dimensional reduction at the end of the therapy. On the contrary, invasive ductal cancers with central necrosis did not show significant reduction of lesion size, likely due to the lower vascularization within the necrotic area (Table 1). Evaluation of the time/intensity curves did not show any difference.

Table 1 Antero-posterior and transverse diameters variation (Δ) in six patients before and after therapy with Trastuzumab

Patient	Sonovue + Trastuzumab (6 patients)					
	Antero/posterior diameter			Transverse diameter		
	Before	After	Δ	Before	After	Δ
1	12	8	4	42	20	22
2	18	13	5	21	15	6
3	16	12	4	23	18	5
4	17	15	2	34	36	−2
5	16	17	−1	32	33	−1
6	12	10	2	25	19	6

Table 2 Nine patients underwent CE ultrasound before and after pre-surgical chemotherapy following different schemes

Chemotherapy	Number
Capecitabine	1
Capecitabine + Vinorelbine	1
Capecitabine + Vinorelbine + LHRH analogue	2
Capecitabine + Vinorelbine + hormonotherapy	1
Epirubicine + Cisplatin + Fluorouracil	1
Herceptin + Vinorelbine	1
Herceptin + Vinorelbine + therapy endocrine with decapeptyl	2

Five out of six patients also underwent CE MR, which showed mean maximum antero-posterior and transverse diameter of lesions pre-therapy of 32.8 (range 24–50)

and 30 mm (range 15–50). The same diameters post-therapy were 27 (range 14–35) and 23.8 mm (range 20–31), respectively. Due to organizational problems, this clinical project was interrupted.

From these results, we went further and started a new, still ongoing, study, designed to evaluate if the dimensional reduction of lesions (as seen in B-mode ultrasound) is associated with a reduction in microcirculation (as shown by the area under the curve in CE ultrasound)[7], compared to the histological specimen report. Furthermore, according to our first results indicating that a wide necrotic area indicates poor vascularization and a low likelihood of response to chemotherapy, we want to assess if the CE ultrasound finding of necrosis can predict the response to pre-surgical chemotherapy. In addition we want to compare the areas under the curves to show the differences before and after presurgical chemotherapy, if any. Eventually we also want to evaluate if there is correspondence between the B-mode finding of complete response (CR) to therapy and the CE ultrasound finding of residual vascularization, as an indicator of partial response (PR).

This study has enrolled nine patients to date to undergo pre- and post-neoadjuvant therapy CE ultrasound, with the aim of predicting the response to pre-surgical chemotherapy performed with different schemes (Table 2). In conclusion, CE ultrasound does not add additional information to B-mode ultrasound in differentiating breast lesions[8–10], but it is a promising tool for evaluating the response to pre-surgical chemotherapy of breast cancer lesions. Further studies are needed to assess new machine settings evaluating the contrast enhancement of lesions in order to give a precise measurement and to predict response to therapy[11], based on ultrasound and CE ultrasound findings.

References

[1] Madjar H, Prompeler HJ, Del Favero C, Hackeloer BJ, Llull JB. A new Doppler signal enhancing agent for flow assessment in breast lesions. Eur J Ultrasound 2000; 12: 123–30.

[2] Wilson AR. Contrast-enhanced breast ultrasound. The clinical context. Eur Radiol 2001; 11 (Suppl 3): E35–40 (no abstract available).

[3] Alamo L, Fischer U. Contrast-enhanced color Doppler ultrasound characteristics in hypervascular breast tumors: comparison with MRI. Eur Radiol 2001; 11: 970–7.

[4] Stuhrmann M, Aronius R, Schietzel M. Tumor vascularity of breast lesions: potentials and limits of contrast-enhanced Doppler sonography. AJR Am J Roentgenol 2000; 175: 1585–9.

[5] Rizzatto G, Martegani A, Chersevani R *et al*. Importance of staging of breast cancer and role of contrast ultrasound. Eur Radiol 2001; 11 (Suppl 3): E47–51 (no abstract available).

[6] Kim SW, Park SS, Ahn SJ *et al*. Identification of angiogenesis in primary breast carcinoma according to the image analysis. Breast Cancer Res Treat 2002; 74: 121–9.

[7] Vallone P, D'Angelo R, Filice S *et al*. Color-Doppler using contrast medium in evaluating the response to neoadjuvant treatment in patients with locally advanced breast carcinoma. Anticancer Res 2005; 25: 595–9.

[8] Kook SH, Kwag HJ. Value of contrast-enhanced power Doppler sonography using a microbubble echo-enhancing agent in evaluation of small breast lesions. J Clin Ultrasound 2003; 31: 227–38.

[9] Caruso G, Ienzi R, Cirino A *et al*. Breast lesion characterization with contrast-enhanced US. Work in progress. Radiol Med (Torino) 2002; 104: 443–50 (English, Italian).

[10] Schroeder RJ, Bostanjoglo M, Rademaker J, Maeurer J, Felix R. Role of power Doppler techniques and ultrasound contrast enhancement in the differential diagnosis of focal breast lesions. Eur Radiol 2003; 13: 68–79.

[11] Schott AF, Roubidoux MA, Helvie MA *et al*. Clinical and radiologic assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. Breast Cancer Res Treat 2005; 92: 231–8.