

cells that have been conveyed to that organ by the arteries [3]. Several theories have been postulated to account for the low incidence of metastases to the spleen compared to other parenchymatous organs [4], including a possible role of spleen contractions in forcing the blood from the sinusoids into the splenic vein which keeps tumour cells in constant motion.

The 2 patients we describe here had spleen metastases from ovarian and colonic cancer in the absence of other distant organ involvement. These unusual presentations of advanced disease raise the question of whether an underlying condition may represent a risk factor for spleen colonisation in subjects with solid tumours. Both patients had liver cirrhosis causing portal hypertension. When the portal venous pressure rises, blood stasis, retrograde blood flow and diversion of portal blood into systemic veins, in an attempt to decompress the portal system, can occur. We suggest, that in such conditions, a neoplastic embolus may reach the spleen via the mesenteric veins and by retrograde blood flow in the splenic vein. Moreover, implantation of neoplastic cells may be facilitated by blood stasis which increases the time of contact with the splenic tissue. The 2 cases described here seem to support this hypothesis. Patient 1 had primary ovarian cancer involving the sigmoid colon and patient 2 had a primary tumour of the descending colon; the venous system of the left region of the colon drains into the portal circulation via the inferior mesenteric vein which enters the splenic vein.

Whether neoplastic cells from tumours draining into the portal system can more easily seed the spleen in patients with portal hypertension needs to be confirmed. However, based on our experience, we suggest a more careful evaluation of the spleen at intervention and during follow-up in these subjects.

3 cm [1–3] or as part of induction chemoradiotherapy [4]. Moreover, the response to induction chemo(radio)therapy may be used as a prognostic factor [5, 6].

Since 1990, we have performed a prospective study of pre-operative induction chemotherapy in patients with different stages of breast cancer. After clinical examination, mammography, ultrasound and cytological proof of the primary tumour, the patients were treated with cyclophosphamide 100 mg/m<sup>2</sup> orally days 1–14, doxorubicin 30 mg/m<sup>2</sup> and 5-Fluorouracil 600 mg/m<sup>2</sup> intravenously (i.v.) on days 1 and 8. Courses were repeated every 4 weeks. After two and four courses, the response of the primary tumour was assessed by palpation, mammography and ultrasound. For stable disease or progression after the first two courses, the patient underwent surgery. Responders received another two courses of chemotherapy and then surgery. Standard criteria of response according to the WHO [7] were used. The study is ongoing. However, in a recent analysis, three problems with the evaluation of response were observed in 7 of the 22 patients (Table 1). In patients 1–3, who had major clinical responses, a very small lesion of viable invasive ductal carcinoma (IDC) was seen adjacent to extensive ductal carcinoma *in situ* (DCIS) in the resection material. These findings indicate a discrepancy between clinical and pathological complete remissions, but more importantly a lack of chemosensitivity of DCIS. Since the extent of DCIS is not predicted by pre-chemotherapy cytology nor expected from the distribution of mammographic microcalcifications [8, 9], extensive DCIS may still be found in resection material after a major response to induction chemotherapy of the invasive tumour.

1. Berge T. Splenic metastases: frequencies and patterns. *Acta Pathol Microbiol Scand* 1974, 82, 499–506.
2. Morgenstern L, Rosenberg J, Geller SA. Tumors of the spleen. *World J Surg* 1985, 9, 468–476.
3. Marymount JH Jr, Gross S. Patterns of metastatic cancer in the spleen. *Am J Clin Pathol* 1963, 40, 58–60.
4. Klein B, Stein M, Kuten A, et al. Splenomegaly and solitary spleen metastasis in solid tumors. *Cancer* 1987, 60, 100–102.

*European Journal of Cancer* Vol. 31A, No. 11, pp. 1886–1887, 1995.  
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0959-8049(95)00378-9

## Problems with the Evaluation of Response After Induction Chemotherapy in Breast Cancer

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INDUCTION CHEMOTHERAPY has become part of the standard treatment of locally advanced breast cancer. Recently, it has also been used to induce "lumpectability" in tumours larger than

Table 1. Patients' characteristics

Patient	Clinical stage	Response	Surgery	Histopathology	
1	T2N2 (2.5 cm)	CR	L*	DCIS	IDC
2	T1N2 (2 cm)	CR	Q*	DCIS	IDC
3	T4bN2 (6 cm)	PR (1.8 cm)	M	DCIS	IDC
4	T2N1 (4 cm)	CR	L*	—	IDC
5	T1N2 (1.5 cm)	MR (1.1 cm)	L*	—	ILC
6	T2N0 (4 cm)	MR (2.1 cm)	L*	LCIS	ILC
7	T4cN1 (5 cm)	PR (1.4 cm)	M	—	ILC

CR, complete response; PR, partial response; MR, minor response; L, lumpectomy; Q, quadrantectomy; M, radical mastectomy; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma. \*After ultrasound localisation.

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Received 13 Mar. 1995; accepted 16 May 1995.

A second problem, related to the discrepancy between clinical and pathological complete remission, is the localisation of the prechemotherapy site of the tumour in a case of clinical complete remission (CR). Patient 4 had obtained a clinical CR and underwent lumpectomy after ultrasound localisation of a doubtful remaining lesion. In the margin of the lump, a very small amount of viable IDC was found, and more IDC in the mastectomy specimen.

The third problem was a major discrepancy between the clinical and pathological response. 3 patients (5–7) had a small lesion after induction chemotherapy. In 2 patients, a lumpectomy and in 1 patient a mastectomy was performed, which were irradiated because of the presence of multifocal tumour rests. In all patients, invasive lobular carcinoma (ILC) was found, which is known for its multicentric diffuse growth pattern [10, 11].

Although there have been reports on the discrepancy between clinical and pathological evaluations of response after induction chemotherapy in breast cancer [1, 12], our experience indicates a cautious approach should be taken in the use of chemotherapy to induce "lumpectability", and it is recommended that the response is verified pathologically, especially in patients with CIS and/or ILC.

*European Journal of Cancer* Vol. 31A, No. 11, pp. 1887–1888, 1995.  
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0959-8049(95)00397-5

## Sequential Chemotherapy, Beta Interferon, Retinoids and Tamoxifen in the Treatment of Metastatic Breast Cancer. A Pilot Study

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CHEMOTHERAPY (CT) for metastatic breast cancer remains palliative, and no clear therapeutic strategy has yet been established for responders with subclinical minimal residual disease. *In vitro* studies have shown that interferons (IFN) and retinoids inhibit the growth of oestrogen receptor positive (ER+) and negative (ER-) breast cancer cell lines [1, 2], and sensitise them to the antiproliferative action of anti-oestrogens through the enhancement of oestrogen receptors [3–6].

This rationale led us to undertake a phase II pilot study to explore the attractive working hypothesis of administering two non-cross-resistant CT regimens, followed by maintenance therapy, with  $\beta$ -IFN, retinoids and tamoxifen (TAM) in a group of patients with poor prognosis metastatic breast cancer. Eligibility criteria included pathologically documented measurable or evaluable breast cancer; age <75 years; performance status <3; no anthracycline chemotherapy; recovery from previous radiotherapy and/or CT with WBC count >3500 mm<sup>3</sup>, platelet count >100 000 mm<sup>3</sup>; normal kidney and cardiovascular function and written informed consent. Induction CT was 4-epidoxorubicin 60 mg/m<sup>2</sup>/day 1, cyclophosphamide 500 mg/m<sup>2</sup>/day 1, vincristine 2 mg day 1, 5-fluorouracil 500 mg/m<sup>2</sup> days 1 and 8, prednisone 50 mg days 1–5, and this was repeated every 3 weeks for six courses, followed by mitomycin-c and mitoxantrone 10 mg/m<sup>2</sup>, methotrexate 40 mg/m<sup>2</sup> day 1 for two courses every 4 weeks. Maintenance therapy for responders was  $\beta$ -IFN  $1 \times 10^6$  IU/m<sup>2</sup> three times a week, retinyl palmitate 50 000 IU twice daily, TAM 10 mg three times daily, until disease relapse.

Responses and toxicities were categorised according to WHO criteria. 36 patients were enrolled in the trial from January 1987 to January 1992. Median age was 61 years (range 37–74); 4 were premenopausal and 32 postmenopausal. Median disease-free interval was 19 months (range 1–28) for 27 patients, while 9 patients had metastases at the time of diagnosis. All patients had

1. Bonadonna G, Veronesi U, Brambilla C, *et al.* Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. *J Natl Cancer Inst* 1990, **82**, 1539–1545.
2. Mauriac L, Durand M, Avril A, Dilhuydy J-M. Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. *Ann Oncol* 1991, **2**, 347–354.
3. Jones AL, Smith IE, O'Brien MER, *et al.* Phase II study of continuous infusion fluorouracil with epirubicin and cisplatin in patients with metastatic and locally advanced breast cancer: an active new regimen. *J Clin Oncol* 1994, **12**, 1259–1265.
4. Jacquillat C, Weil M, Baillet F, *et al.* Results of neoadjuvant chemotherapy and radiation therapy in the breast-conserving treatment of 250 patients with all stages of infiltrative breast cancer. *Cancer* 1990, **66**, 119–129.
5. Bonadonna G, Valagussa P, Brambilla C, *et al.* Response to primary chemotherapy increases rates of breast preservation and correlates with prognosis. *Proc Am Soc Clin Oncol* 1994, **13** 107, Abstr. 230.
6. Khayat D, Weil M, Auclerc G, *et al.* Clinical relevance of tumor regression in neoadjuvant chemotherapy in breast cancer revisited. *Proc Am Soc Clin Oncol* 1994, **13**, 75, Abstr. 99.
7. WHO (1979). Handbook of Reporting Results of Cancer Treatment. Offset publication No 48. World Health Organization, Geneva.
8. Holland R, Connolly JL, Gelman R, *et al.* The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. *J Clin Oncol* 1990, **8**, 113–118.
9. Holland R, Hendriks JHCL, Verbeek ALM, *et al.* Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma *in situ*. *Lancet* 1990, **335**, 519–522.
10. Helvie MA, Paramagul C, Oberman HA, *et al.* Invasive lobular carcinoma; imaging features and clinical detection. *Invest Radiol* 1993, **28**, 202–207.
11. Poen JC, Tran L, Juillard G, *et al.* Conservation therapy for invasive lobular carcinoma of the breast. *Cancer* 1992, **69**, 2789–2795.
12. Feldman LD, Hortobagyi GN, Buzdar AU, *et al.* Pathological assessment of response to induction chemotherapy in breast cancer. *Cancer Res* 1986, **46**, 2578–2581.

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Revised 12 Jun. 1995; accepted 7 Jul. 1995.