PERGAMON

European Journal of Cancer 38 (2002) 2371–2374

European Journal of Cancer

www.ejconline.com

The surgical management of patients following neoadjuvant chemotherapy for locally advanced breast cancer

P. Sauven*

The Breast Unit, Chelmsford and Essex Centre, Chelmsford CM2 0QH, UK

Received 20 September 2001; received in revised form 9 April 2002; accepted 11 April 2002

Abstract

The aim of this study was to evaluate the role of surgery in patients who achieve a complete clinical response (cCR) to neoadjuvant chemotherapy for locally advanced breast cancer. A retrospective study of patients with either large central (T2 >30 mm, N0 or N1, M0) or locally advanced (T3, N0 or N1, M0) tumours who received neoadjuvant chemotherapy followed by surgery to the breast and axilla and postoperative radiotherapy. All patients had operable disease at presentation. A total of 133 patients were included. Overall, 43 (32%) patients achieved a cCR following chemotherapy. Of these, 19 patients had no pathological evidence of disease in the breast (pCR) or on imaging or core biopsy and these patients received only adjuvant radiotherapy to the breast. A further 5 patients had no pathological evidence of cancer following breast surgery. 126 patients had an axillary clearance. Increasing response to chemotherapy was related to fewer pathologically involved nodes, but 7 of 24 (29%) patients with a pCR still had evidence of axillary metastases. This is the principal conclusion of the study at the present time. The patients were followed-up for a median of 30 months (range 5–83 months) with a local recurrence rate of 3.8%. There was no difference in either distant recurrence-free or overall survival between patients experiencing a pCR and the remainder.

Keywords: Surgical management; Breast cancer; Chemotherapy; Locally advanced; Neoadjuvant

1. Introduction

The long-term aim of this study was to assess whether patients who achieve a complete pathological response to neoadjuvant chemotherapy can be safely managed with subsequent adjuvant radiotherapy alone to the breast and also to examine the role of axillary surgery following neoadjuvant chemotherapy.

Primary (neoadjuvant) chemotherapy has been demonstrated to be effective in diminishing tumour size in locally advanced disease making it possible to undertake conservation surgery in place of mastectomy [1]. Whilst in theory it had been hoped that the introduction of neoadjuvant chemotherapy might improve both local control and overall survival there is no evidence to support this [2].

The role of surgery following neoadjuvant chemotherapy is confusing with many authors urging caution as regards the use of radiotherapy alone in place of breast surgery following chemotherapy [3,4]. In a review of all published studies Kuerer and colleagues noted that the local recurrence rates were highest in those studies in which radiotherapy was the only form of loco-regional treatment [6]. In none of these studies, however, was there an attempt to identify patients by pathological response.

Similarly, the role of axillary surgery following chemotherapy has been questioned on the basis that a complete response in the breast is likely to be associated with a similar down-staging of axillary disease [5,7]. Both Vlastos and Kuerer and colleagues have proposed that axillary surgery be omitted if the axilla is clinically and ultrasonically negative on the basis that these patients have only minimal disease [5,8]. Nevertheless, in both authors series, 48% of axillae that were clinically and ultrasonically negative had subsequent pathological evidence of nodal metastases.

2. Patients and methods

The policy in our unit during the period of this study was to offer neoadjuvant chemotherapy as an alternative

* Tel.: +44-1245-513405; fax: +44-1245-514024.
E-mail address: paul.sauven@meht.nhs.uk (P. Sauven).

0959-8049/02/$ - see front matter
PII: S0959-8049(02)00243-5

Table 1
Type of surgery according to clinical response to neoadjuvant chemotherapy

Clinical response	DXT[a] alone	Mastectomy	Mastectomy (Pt choice)	Wide excision	None	Total
Complete response	19	10	2	12		43
Partial response		10		9	1	20
No change		47	1	13	1	62
Progressive disease		8				8
Total	19 (14%)	75 (56%)	3	34 (26%)	2	133

[a] DXT, radiotherapy.

to mastectomy in women with large central (T2 >30 mm, N0 or N1, M0) or locally advanced (T3, N0 or N1, M0) tumours. Only patients with operable primary tumours at the time of diagnosis were included and those with inoperable tumours or metastatic disease at presentation have been excluded. The diagnosis was confirmed with a core biopsy and patients were screened for metastatic disease. Following chemotherapy, patients were assessed clinically and radiologically principally using ultrasound (US) and mammography with magnetic resonance imaging (MRI), when available, for radiologically-occult tumours. Response to chemotherapy was graded according to the International Union Against Contre Cancer (UICC) criteria as a clinical complete response (cCR), a partial response if the tumour size decreased by 50% (measured as the product of two perpendicular diameters) or more (PR), no change (NC), or progressive disease (PD) [9]. Those patients who achieved a complete clinical and radiological response (no evidence of tumour on clinical, mammographic or US examination) did not have immediate surgery to the breast, but underwent multiple labelled core biopsies of the breast, centrally and in all quadrants, at the time of axillary surgery. If these subsequently demonstrated no invasive or *in-situ* cancer, the patients were deemed to have had a pCR and proceeded to undergo radiotherapy alone to the breast. All patients had an axillary clearance (except 4 who refused and 3 who had had a previous contra-lateral axillary clearance) and all received postoperative adjuvant radiotherapy to the breast or chest wall.

Descriptive statistics and log rank survival analyses were performed with the Statistical Package for the Social Studies (SPSS) Statistical software.

3. Results

A total of 133 patients received neoadjuvant chemotherapy between October 1994 and September 2000 for large, central (T2 >30 mm, N0 or N1, M0) or locally advanced (T3, N0 or N1, M0) tumours. The majority ($n=122$) received six cycles of doxorubicin (Adriamycin) and cyclophosphamide, the remainder ($n=11$) six cycles of cyclophosphamide, methotrexate and 5-fluorouracil.The mean pretreatment tumour size was 49.28 mm standard error of the mean (S.E.M. 1.50) and post-treatment was 24.01 mm (S.E.M. 1.73).

The overall clinical response to chemotherapy was cCR in 43 patients (32%), PR in 20 (15%), NC in 62 (47%) and PD in 8 (6%). The surgical management of these patients is summarised in Table 1. Overall, 55 of the 133 patients (42%) retained their breast and two patients declined surgery.

In 19 patients, core biopsies undertaken at the time of axillary surgery confirmed a complete pathological response (pCR) with no evidence of either invasive or *in-situ* disease following chemotherapy. These patients had no further surgery. In 10 patients with a complete clinical response, a mastectomy was recommended on the basis of radiological evidence of residual disease or diffuse microcalcification. One of these patients was subsequently proven to have a pCR, as were 3 patients with a cCR recommended to have a wide excision and 1 of the patients who elected to have a mastectomy by choice. The true apparent pCR rate was thus 18%.

An axillary clearance was undertaken in 126 of the 133 patients. The pathological nodal status of these patients is summarised in Table 2.

There was a significant relationship between increasing clinical response to chemotherapy and pathological node negativity ($Chi^2=10.53$, degrees of freedom (df) $=3$, $P>0.01$). Perhaps surprisingly, even in the 24 patients with a pCR in the breast, 7 (29%) had evidence of axillary nodal disease, 1 with more than three involved nodes.

Table 2
Pathological nodal status of patients according to clinical response to neoadjuvant chemotherapy

Clinical response	Node-negative (%)	1–3 nodes involved	$\geqslant$4 nodes involved	Total positive nodes (%)	Total
Complete response	30 (73)	8	3	11 (27)	41
Partial response	10 (56)	7	1	8 (44)	18
No change	24 (41)	17	18	35 (59)	59
Progressive disease	5 (63)	1	2	3 (38)	8
Total	69 (55)	33	24	57 (45)	126

The patients were followed-up for a median of 30 months (range 5–83 months). A total of 33 initial recurrences were recorded in 30 patients during this period of follow-up with the site of first relapse being local in 5 patients, regional in 1 and distant in 27. This represents a local recurrence rate of 3.8% at 30 months. Only 1 patient with a pCR relapsed locally. A course of radiotherapy had been agreed at the multidisciplinary meeting following final assessment postchemotherapy, but this was delayed for 13 weeks for logistic reasons in place of the planned 4 weeks. No patients had uncontrolled local disease.

There was no significant difference in either disease-free or overall survival according to the clinical response to chemotherapy and neither was there any evidence of a survival benefit for those in pCR compared with the remainder. The patients with a pCR treated by radiotherapy alone to the breast were analysed for both recurrence-free survival and overall survival compared with the remainder, but there was no significant differences in either group.

4. Discussion

4.1. Response

Neoadjuvant chemotherapy has an established role in the management of patients presenting with large or locally advanced breast cancers and results in a significant number of patients having their tumours downstaged sufficiently to avoid mastectomy [1]. The clinical response rate to chemotherapy in this series is similar to other published studies although strict adherence to the UICC criteria reduces the number of partial responders. Many authors have included patients with less than a 50% reduction in tumour size as responders and comparison between studies is not always possible [10–12]. The 18% pathological complete response rate is however significantly higher than the 9.4% reported in the National Surgical and Adjuvant Breast and Bowel Project (NSABP)-B18 study, but is similar to the 20% reported in a study from Aberdeen which represents the highest pCR rate in any reported series [1,13].

Assessment of response remains problematic. Although clinical assessment remains important, it is of limited benefit in defining an objective response. All patients in our study had mammographic and US assessment, both prior to and following chemotherapy, but at least 10% patients had tumours that were not visualised. MRI was available for 6 such patients later in the study and reports suggest that with increasing experience, MRI is likely to be helpful [14]. Nevertheless, it is still not generally possible to undertake MRI-guided core biopsies in the manner that can be performed without difficulty ultrasonically or with digital mammography as we have done.

4.2. Surgery

Singletary and colleagues proposed criteria for breast conservation following neoadjuvant chemotherapy based on a study of careful pathological assessment of tumour response [15]. These criteria are essentially similar to those in routine use for the surgical management of early breast cancer and include a tumour size post-treatment of <5 cm, absence of extensive suspicious microcalcification, and no known evidence of multicentricity. Our own criteria closely matched these and permitted 42% of patients to initially retain their breast.

4.3. Local recurrence

The NSABP-B18 trial, which recruited more patients than all of the other published randomised studies combined, demonstrated no significant differences in either the local or distant disease-free survival rates between the two treatment arms and there is no evidence to suggest that neoadjuvant chemotherapy is either inferior or superior to standard postoperative adjuvant treatment options [1]. The period of follow-up in our series is too short to be confidant of the long-term outcome, but the 3.8% local recurrence rate at a median of 30 months appears commensurate with other studies [1,16,17]. In particular, there is no evidence that the treatment of pCR patients in our series by radiotherapy alone has resulted in an increased rate of early local recurrence.

4.4. Axilla

Neoadjuvant chemotherapy would appear to be less effective at downstaging axillary disease than that in the primary tumour and the NSABP-B18 study demonstrated that there were 37% fewer patients with pathological involved nodes in those receiving preoperative chemotherapy in comparison with those receiving it postoperatively. Two other groups have used clinical and US assessment of the axillary nodal status following neoadjuvant chemotherapy, but both report an incidence of 48% pathological involved nodes in patients assessed as being node-negative [5,6]. The M.D. Anderson reported a 28% incidence of pathological involved nodes in patients with a pCR which is identical to this series [6]. They have commenced a prospective study to evaluate the role of radiotherapy to the axilla in place of surgery as the majority of these patients will have minimal disease. The current study predates the introduction of sentinel node techniques to our unit, but the sensitivity of this technique under these circumstances is questionable. Unpublished data from NSABP-B18 suggests a fall in sensitivity from 95 to 75% when used following neoadjuvant chemotherapy. Several prospective studies are in progress, but current evidence suggests that even patients with a pCR should have axillary surgery.

4.5. Survival

The NSABP-B18 study showed no difference in overall survival between patients treated with either pre- or post-operative chemotherapy [2]. The outcome was significantly better in the former group when there was a pCR compared with a cPR with 5-year relapse-free survival rates of 85.7 and 68.1%, respectively [2]. This finding was broadly supported by a much smaller study from Aberdeen in which patients with a pCR had a 5-year survival of 74% compared with 36% for pPR [13]. The number of events in the present study is insufficient to demonstrate a survival benefit for patients experiencing a pCR.

4.6. Quality of life

This study did not address the complex psycho-social issues raised. All patients considered for neoadjuvant chemotherapy were seen in a joint oncology clinic and informed that there was no evidence to suggest a survival advantage for either treatment option. It thus became essentially an issue of identifying those women for whom the chance of breast conservation was paramount.

5. Conclusions

The role of surgery in patients with locally advanced breast cancer is to ensure good local control of the cancer. This study demonstrates that a high pathological complete response rate to neoadjuvant chemotherapy can be achieved and other studies have shown that such a response identifies those patients likely to have a better overall prognosis. Provided that a pCR can be reliably confirmed, these patients may be safely managed by radiotherapy alone to the breast. Nevertheless, a significant proportion of these patients will have axillary nodal metastases and, at present, appropriate axillary surgery should remain the 'standard of care'.

Acknowledgements

I would like to acknowledge the invaluable support of Dr Bill Pratt, Dr Saad Tahir and Dr Neville Davidson as the Clinical Oncologists involved in the management of these patients and to all members of the Multidisciplinary Team at the Breast Unit. I am grateful to Jim Kedilty and Sue Mason for database management and Dr Chris Smith for statistical support.

References

1. Fisher B, Brown A, Mamounas E, *et al*. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997, **15**, 2483–2493.
2. Fisher B, Bryant J, Wolmark N, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998, **16**, 2672–2685.
3. Sapunar F, Smith IE. Neoadjuvant chemotherapy for breast cancer. *Ann Med* 2000, **32**, 43–50.
4. George ML, Hale PC, Gumpert JRW, Hogbin BM, Deutsch GP, Yelland A. The use of neoadjuvant CMF to avoid mastectomy. *Eur J Surg Oncol* 1999, **25**, 50–53.
5. Vlastos G, Fornage BD, Mirza NQ, *et al*. The correlation of axillary ultrasonography with histologic breast cancer downstaging after induction chemotherapy. *Am J Surg* 2000, **179**, 446–452.
6. Kuerer HM, Newman LA, Fornage BD, *et al*. Role of axillary lymph node dissection after tumor or downstaging with induction chemotherapy for locally advanced breast cancer. *Ann Surg Oncol* 1998, **5**, 673–680.
7. Danforth Jr. DN, Zujewski J, O'Shaughnessy J, *et al*. Selection of local therapy after neoadjuvant chemotherapy in patients with stage IIIA,B breast cancer. *Ann Surg Oncol* 1998, **5**, 150–158.
8. Kuerer HM, Hunt KK, Newman LA, Ross MI, Ames FC, Singletary SE. Neoadjuvant chemotherapy in women with invasive breast carcinoma: conceptual basis and fundemental surgical issues. *J Am Coll Surg* 2000, **190**, 350–363.
9. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Powles TJ, Hickish TF, Makris A, *et al*. Randomised trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. *J Clin Oncol* 1995, **13**, 547–552.
11. Smith IE, Walsh G, Jones A, *et al*. High complete remission rates with primary neoadjuvant infusional chemotherapy for large early breast cancer. *J Clin Oncol* 1995, **13**, 424–429.
12. Bonadonna G, Valagussa P, Brambilla C, *et al*. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. *J Clin Oncol* 1998, **16**, 93–100.
13. Eltahir A, Heys SD, Hutcheon AW, Sarkar TK, Smith LG, Ah-See AK, Eremin O. Treatment of large and locally advanced breast cancers using neoadjuvant chemotherapy. *Am J Surg* 1998, **175**, 127–132.
14. Drew PJ, Kerin MJ, Mahapatra T, Malone JR, Monson JRT, Turnbull LW, Fox JN. Evaluation of response to neoadjuvant chemotherapy for locally advanced breast cancer with dynamic contrast-enhanced MRI of the breast. *EJSO* 2001, **27**, 617–620.
15. Singletary SE, McNeese MD, Hortobagyi GN. Feasibility of breast conservation surgery after induction chemotherapy for locally advanced breast cancer. *Cancer* 1992, **69**, 2849–2852.
16. Scholl SM, Asselain B, Beuzeboc P, *et al*. Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumors considered too large for breast conserving surgery. An update (abstract). *Proc Am Soc Clin Oncol* 1995, **14**, A200.
17. Makris A, Powles TJ, Ashley SE, *et al*. A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. *Ann Oncol* 1998, **9**, 1179–1184.