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Editorial

Chemotherapy For Metastatic Breast Cancer — When is Enough Enough?

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THE PRIMARY goals of treatment in metastatic breast cancer are palliative — to improve length and quality of life without prospect of cure. Randomised trials comparing chemotherapy with no anticancer treatment in women with metastatic breast cancer have not been published. Whether chemotherapy improves length or quality of life in metastatic breast cancer therefore remains a moot point. Trials directly addressing this question are unlikely to be carried out in the future, since evidence of survival benefit in early disease [1] and of tumour shrinkage and improved quality of life in advanced disease [2] have resulted in the adoption of chemotherapy as a standard treatment. Acknowledging that chemotherapy will be given to most women with metastatic breast cancer, how long should it be given for?

Gregory and associates contribute to the data on this question with a small well-conducted trial reported in this issue of the journal [3] (pp. 2194–2197). 107 patients with an objective tumour response or stable disease after six cycles of combination chemotherapy were randomised to stop or continue with the same treatment; 100 of the 107 were included in the analysis. Progression-free survival ($P < 0.01$) and response duration ($P < 0.025$) were substantially longer in the group continuing chemotherapy. Overall survival was also longer in those who continued chemotherapy (median survivals of 13 versus 10.5 months), but this difference failed to reach conventional statistical significance ($P > 0.1$). The authors conclude that continuing chemotherapy for longer than 6 months is unlikely to prolong survival. Is this conclusion supported by the data?

The interpretation of 'negative' results from small trials, particularly those with an active control arm, has received considerable attention [4–6]. The lack of a statistically significant difference between treatments is not proof that the treatments are the same. In fact, the results of this trial are entirely consistent with the results of other trials addressing the same question, namely that a longer duration of treatment leads to longer survival.

A systematic review identified three trials indexed in Medline from 1966 to 1996 which compared shorter with longer durations of the same chemotherapy in women with advanced breast cancer [2, 7–10]. Meta-analysis of these three trials including 666 women indicates a survival advantage for women randomised to longer durations of chemotherapy ($P = 0.01$ for weighted combination of log-rank tests). Median survival was 23% longer in women randomised to longer durations of chemotherapy, a difference identical in size to that found in the Gregory trial, but with the additional precision afforded by a larger sample. All four trials and the combined results are summarised in Figure 1. The addition of the present data reinforces the findings of the previous studies.

While this survival benefit is modest, it applies to many women, since metastatic breast cancer is unfortunately a common problem. It must also be considered in the knowledge that small increments in survival duration are valued highly by women with breast cancer [11]. Conversely, any prolongation of survival must be weighed against the additional subjective toxicity of continued chemotherapy. Gregory and associates did not detect expected differences in toxicity and comment that formal assessment of quality of life is necessary to answer this question.

In the one trial where quality of life was measured, those who received more cycles of chemotherapy reported better quality of life (and lived longer) than those who received fewer cycles of chemotherapy [2, 9]. This counterintuitive result implies that the subjective side-effects of chemotherapy were outweighed by a reduction in cancer-related symptoms.

The combined evidence from all these trials supports a policy of continuing chemotherapy in the absence of disease progression or prohibitive toxicity. The question of what constitutes prohibitive toxicity should be answered by the patient and doctor together, guided by the protocols followed in these trials. While this evidence is directly applicable to women with metastatic breast cancer, it may also provide guidance in the treatment of other types of cancer where such trials have not yet been done.

Finally, these results also offer an important insight into the fundamental question of whether chemotherapy itself prolongs survival in metastatic breast cancer. It is unlikely that a few cycles of chemotherapy shorten survival, yet continuing therapy more than a few cycles extends the survival obtained

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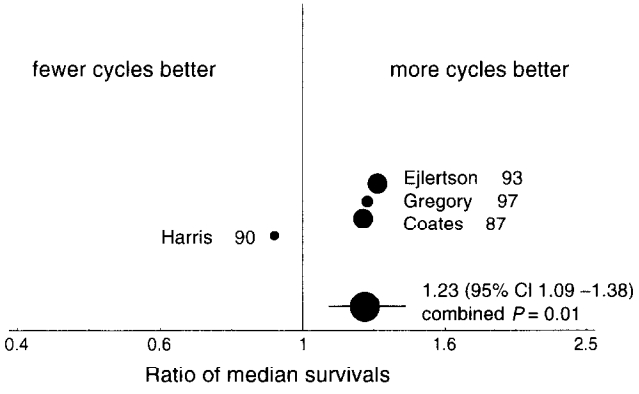

Author, Year	Experimental arm (exp)	Control arm (con)	Subjects	Median Survival (months) Exp	Con	Exp/Con	Logrank *P*–value	Reference
Ejlertson B, 93	FEC × 24 + tam	FEC × 8 + tam	318	23	18	1.28	0.03	8
Coates A, 87	continuous AC or CMF	intermittent AC or CMF	305	11	9	1.22	0.14	2,9
Gregory R, 97	MMM or VAC or VEC × 12	MMM or VAC or VEC × 6	100	13	11	1.24	0.26	3
Harris A, 90	continuous Mitoxantrone	Mitoxantrone × 4	43	11	12	0.92	NS	10
Weighted Combination	More Cycles	Fewer Cycles	766			1.23	0.01	

Figure 1. Meta-analysis of published trials of more versus fewer cycles of chemotherapy for metastatic breast cancer. Exp/Con is the ratio of the median survival in the experimental arm to that in the control arm. This is shown in the treeplot as a closed circle, the size of which is proportional to the number of patients in the trial. The aggregate results are weighted combinations of the ratios of median survivals, with 95% confidence intervals based on the variability between studies, and of the log-rank test *P* values, with the weight for each trial proportional to its number of subjects: A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; E, epirubicin; tam, tamoxifen; MMM, mitoxantrone, methotrexate, mitomycin; V, vincristine; NS, reported as 'not significant' in the primary publication.

with the few. This is strong evidence that chemotherapy prolongs survival in metastatic breast cancer, and is consistent with the data (but not the conclusions) of Gregory and associates.

1. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992, **339**, 1–14, 71–85.
2. Coates A, Gebski V, Bishop JF, *et al.* Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. *N Engl J Med* 1987, **317**, 1490–1495.
3. Gregory RK, Powles TJ, Chang J, Ashley S. A randomised trial of six versus twelve courses of chemotherapy in metastatic carcinoma of the breast. *Eur J Cancer* 1997, **33**, 2194–2197.
4. Freeman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial: survey of 71 "negative trials". *N Engl J Med* 1978, **299**, 690–694.
5. Glaholm J, Mort C, Ashley S, Yarnold JR. Duration of chemotherapy in advanced breast carcinoma. *Lancet* 1990, **335**, 1033.
6. Altman DF, Bland JM. Absence of evidence is not evidence of absence. *BMJ* 1995, **311**, 485.
7. Stockler M, Wilcken N, Ghersi D, Simes J. *The Management of Advanced Breast Cancer: Systematic Reviews of Randomised Controlled Trials Regarding the Use of Cytotoxic Chemotherapy and Endocrine Therapy.* Australian NH&MRC National Breast Cancer Centre, 1996.
8. Ejlertsen B, Pfeiffer P, Pedersen D, *et al.* Decreased efficacy of cyclophosphamide, epirubicin and 5-fluorouracil in metastatic breast cancer when reducing treatment duration from 18 to 6 months. *Eur J Cancer* 1993, **29A**, 527–531.
9. Coates A, Byrne M, Bishop JF, Forbes JF. Intermittent versus continuous chemotherapy for breast cancer. *N Engl J Med* 1988, **318**, 1468.
10. Harris AL, Cantwell BM, Carmichael J, *et al.* Comparison of short-term and continuous chemotherapy (mitoxantrone) for advanced breast cancer. *Lancet* 1990, **335**, 186–190.
11. Coates AS, Simes RJ. Patient assessment of adjuvant therapy in operable breast cancer. In Williams CJ, ed. *Introducing New Treatments for Cancer: Practical, Ethical and Legal Problems.* New York, Wiley and Sons, 1992.