Cancer Research Campaign Breast Study

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The choice of treatment for early cancer of the breast has long been a major point of debate among clinicians. There has been a notable absence of clinical trials giving a clear indication in a particular direction and it has been most difficult to have confidence in their results. The crucial problem has been the small numbers of patients admitted to such trials.

In order to overcome this and other difficulties, more than 300 clinicians from 90 centres accepted an invitation to submit patients to what originally started off as the King's/Cambridge trial and is now known as the Cancer Research Campaign Breast Study. The vast majority of clinicians are from the United Kingdom, but some are from Canada, New Zealand, Scandinavia, Switzerland and the Republic of Ireland. The present author is acting as custodian for their work and is reporting the study on their behalf.

The aim of the trial

We set out to explore two quite different views of the biological behaviour of breast cancer in women. The traditional view is that cancer starting in the breast remains there for some considerable time, spreading directly and by lymphatics to regional lymph nodes. Only at a later date, on the whole, does it spread by the bloodstream to distant sites in bones, lungs and so on. At an early stage in the disease process the best treatment would seem to be removal or destruction of the malignant cells locally by surgical means, or partly by surgery and partly by radiotherapy. These may be termed radical treatments and the one most commonly practised throughout this country is simple mastectomy followed by postoperative radiotherapy (Baum et al., 1972).

The opposing view, which is gathering momentum, is that in so-called 'early' cancer there is already distant dissemination of the disease in many patients. This process of growth of tumour and dissemination may be under the influence of natural defence mechanisms. Anything that depresses the defence mechanisms may be harmful to the patient. It is now known that radiotherapy, as traditionally used in the treatment of breast cancer, depresses local immune reactions and also the reticulo-endothelial system throughout the body (Baum et al., 1972). To avoid the depression of the defence mechanisms a conservative régime was used: simple mastectomy and a watch policy. No further treatment was given unless there were indications of recurrence, for example in the operation scar or in the lymph nodes of the axilla. Simple mastectomy was performed on all patients with Stage I or II cancer of the breast and then they were randomly allocated to either the irradiation group or the watch policy group.

Problems peculiar to breast trials

A clinical trial on the treatment of breast cancer inevitably lasts for a minimum of 15 years from beginning to end. This is made up of a 4-5-year collection period and a follow-up of at least 10 years. Attitudes change about management of the disease and, with increasing knowledge of the biology of breast cancer, views will change at an ever-increasing rate. Clearly, the follow-up cannot be shortened, so every effort must be made to limit the collection period to the shortest time possible. Rapid collection of large numbers can only be achieved in a multicentre trial. Over 2000 patients have been entered into the Cancer Research Campaign Breast Study in under 4 years.

The number of patients required in a clinical trial

Previous controlled trials have suggested that only a small difference is likely to exist between two treatment groups. We felt that the smallest difference which was likely to influence clinicians to prefer one form of treatment to another was about 7 per cent. It is conventional, in regarding a result as being statistically significant, to accept a 1 in 20 risk of the result being due to chance ($P = 0.05$). *Table I* shows the total number of patients required in both treatment groups in order to detect a given true difference at a statistically significant level. It also indicates the numbers required to have a 90, 75 and 50 per cent chance of detecting such true differences. This chance has been termed 'degree of confidence'. If we want to have a 90 per cent chance of detecting a true difference of 7 per cent, then 2000 patients are required within the study. With much smaller numbers, about 750 in all, a true difference of 7 per cent may be detected, but there is only a 50 per cent chance of this happening—a 1 in 2 chance, or the toss of a coin. With still smaller numbers, it is

| Degree of confidence for $P = 0.05$ | Total no. of patients required |
|-----------------------------------|--------------------------------|
| 50%                               | 150 750 1500                   |
| 75%                               | 300 1300 2500                   |
| 90%                               | 450 **2000** 4000               |
| True difference between two treatments | 15% 7% 5%                         |

* *Boag et al. (1971)*

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Fig. 1. Trends shown in the study to date. The horizontal axis indicates number of years of follow-up, the vertical axis percentage of patients alive in the first column and alive with no distant metastases in the second column. Seven hundred patients have been followed up for 2 years and 150 for 3 years.

Theoretically possible for the trial to indicate an advantage in the wrong direction.

Conversely, to show that there is no significant difference between the two therapies can be an important advance. If we could avoid subjecting patients to unnecessary discomfort and occasional morbidity, for example as a result of radiotherapy, then all efforts would be worth while.

Large numbers entered have another great advantage, perhaps the greatest of all. It enables subgroups within the main treatment regimes to be of a reasonable size. An example is in the behaviour of different histological types of tumours. Analysis of a number of patients in the study has shown that more than a third have undifferentiated or anaplastic tumours. These can behave in two quite different and distinctive ways. One illustrates the aggressiveness of the tumour, and a large proportion of women have distant dissemination at an early stage. However, if the patient can respond immunologically to the tumour and if this response is reflected by a round cell or lymphocytic infiltration around the tumour, then their behaviour is quite different. The prognosis is indeed good. The medullary type of tumour is the extreme example of this. It is quite likely that such patients can be harmed by irradiation. This will only be answered as the study progresses. It is almost certainly along these lines of observing the behaviour of subgroups and their responses to treatment that we will be able to tailor the most effective treatment for an individual woman with so-called ‘early’ cancer of the breast.

Results
Since the study has only been under way for 4 years, too few patients have been followed up for too short a time to give meaningful results. As can be seen, in a follow-up of 2000 patients only 700 have been followed up for 2 years and 150 for 3 years. There are, of course, fewer still in the individual stages, I and II. Fig. 1 considers only the two most obvious results of treatment, i.e. survival in the first column, and in the second column, alive but with no recognizable distant metastases. The first statement that can be made from these very preliminary trends is that the
results of the conservative form of treatment (simple mastectomy alone) are no worse than those of radical treatment, which includes postoperative irradiation. Indeed, the figures in the top right-hand graph show a difference approaching statistical significance. It suggests that the occurrence of distant metastases is higher in the group treated with irradiation.

Next are the results in Stage I. Here, there is no particular trend one way or the other at this very early stage. However, when Stage II is considered, where many might have expected that postoperative radiotherapy would have been most beneficial, the trends, to date, do not substantiate this view. The suggestion is that a larger number of people die within 3 years or have distant metastases in the irradiated group than in the watch policy group. It should be noted that the numbers of patients so far followed up over the 3 years are small. We will have to wait and see whether these trends persist with larger numbers of patients followed up for a longer period of time.

It is hoped that this paper gives some insight into the most difficult problem of the organization of a trial on the management of early cancer of the breast and why there is still so much doubt and uncertainty about the best form of management of early cancer of the breast.

References

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