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Early Presentation of Results in Clinical Trials: an Ethical Dilemma for Medicine and Science

The paper 'Adjuvant chemotherapy for medulloblastoma, the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I)', by Tait *et al.* [1], is intriguing and contains several aspects of interest. In the trial, the value of adjuvant chemotherapy was tested in patients receiving radiotherapy for medulloblastoma. The results published in the paper, which appears in the present issue, demonstrate that even for rare tumours, clinical trials can answer relevant questions only through the cooperation of multidisciplinary teams in many centres. The outcome of such a trial, because of its multicentre character, has much wider applicability than results obtained in a single institution. Another interesting aspect of the study is a significant difference in treatment outcome between the large and small centres in favour of the former (56.9 vs. 41.8% 5 year disease-free survival respectively; $P < 0.005$). Such a difference in survival may be the result of differences in patient selection or the more extensive experience in the management of rare tumours which may require complex treatment in larger centres. Nevertheless, the results point to the need for centralization of treatment for rare tumours.

One of the most notable aspects of the trial was its termination at an early stage because it was considered unethical to deprive patients of chemotherapy in view of the significant difference in favour of combined modality treatment shown at early interim analysis. With the longer follow-up, however, the difference became smaller and lost its significance. As a result the study has not been able to determine whether the lack of a significant difference reflects insufficient sample size, ineffective chemotherapy, choice of statistical method or is due to other reasons.

In general, the premature closure of a clinical trial and publication of preliminary data may result in the following consequences:

1. A new therapeutic approach cannot be reliably assessed.
2. Unproven therapy may be adopted as standard practice leading to the use of ineffective yet potentially toxic treatment in a large number of patients outside the setting of a clinical trial.
3. In designing a new trial a suboptimal standard arm may be selected.

The present example of preliminary closure of a trial on ethical grounds is not unique. However, the publication of mature data of this kind is important, particularly since it is more difficult to publish negative results after initial announcements of very promising results. Indeed, final reports are often lacking in such situations. A recent example that has attracted considerable attention [2] is the closure of the US AIDS Clinical Trials Group study in which zidovudine (AZT) has shown a beneficial effect. A critical look at the results of this study reveals that, despite significant differences between the treatment arms, the proportion of patients who have developed AIDS so far was relatively small (only 7% of the total patient population). Theoretically it would not be a surprise if, with longer follow-up, the statistical significance of the difference is lost.

Preliminary publications on the presumed positive effects of adjuvant therapy of common tumours like breast or colon cancer may cause harm in the long term. Assuming that 10% of randomized studies include a therapy that represents benefit and adopting a 5% false-positive rate and 20% false-negative rate, 36% of the reported positive outcomes from clinical trials will be false-positive [3]. When the false-positive rate is raised to 20% because of the frequent and often premature analysis of the data, the proportion of false-positive outcomes rises to 65%.

Even adoption of a 1% false-positive rate in a clinical setting will result in a 14% false-positive rate among all reported positive trials. These far-reaching consequences of early termination of a trial or announcement of preliminary results may outweigh the presumed ethical basis that led to study interruption.

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The Clinical Relevance of Tumour Hypoxia

IT IS generally accepted that oxygen deficiency is a common occurrence in many human tumours. However, to what extent tumour hypoxia influences treatment response is still unclear. A detailed review of the state of knowledge on tumour hypoxia was the subject of a meeting convened by the Radiotherapy Group of the EORTC in Leuven in December 1989. The meeting addressed basic laboratory studies in molecular, cellular and tissue radiobiology, the measurement of tissue hypoxia, and new developments in the field of radiation sensitizers and bioreductive drugs. Clinical studies of methods for eradicating tumour hypoxia and exploiting the presence of hypoxia for new approaches to diagnosis and therapy were also reviewed.

Clinical evidence from some of the early hyperbaric oxygen trials indicates that tumour hypoxia may adversely influence treatment outcome, particularly in cancer of the cervix and head and neck. Recent results suggest that variation in oxygen levels in individual head and neck tumours directly influences treatment outcome. However, tumour heterogeneity is clearly a major confounding factor in the interpretation of clinical trials. In addition to tumour size, efficiency of re-oxygenation and haemoglobin status are probably important determinants of treatment outcome in some situations. Anaemia is clearly an important factor and there is increasing evidence that haemoglobin levels within the normal range can influence prognosis.

The clinical measurement of tumour hypoxia includes the use of *in situ* ultra-fine oxygen electrodes. The observations indicate considerable heterogeneity of oxygenation within individual tumours and even within normal tissues. This type of approach has promise for the identification and possibly classification of tumours where hypoxia has an adverse effect on treatment outcome. However, less invasive techniques for measuring individual variations in the hypoxic status of tumours would have obvious advantages.

In this context, the use of isotopically labelled bioreductive agents for detecting tumour hypoxia shows promise and the phenomenon of bioreductively activated binding of nitroimidazole drugs in hypoxic tissue is under active investigation as a means of localizing iodine-131 for scintigraphic identification of tumour hypoxia *in situ*.

Manoeuvres designed to improve tumour oxygenation include the use of blood flow modifiers for increasing oxygen levels in tumours. The vasoactive drugs flunarizine and nicotinamide significantly reduce the levels of hypoxia in some experimental murine tumours. An alternative approach is to manipulate the binding affinity of oxygen and haemoglobin. Clofibrate, for example, substantially right-shifts the oxy-haemoglobin association curve and increases the radiation sensitivity of some murine tumours.