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Comments and Critique

Quality Control in Chemotherapy

IN TRIALS of cancer chemotherapy, the important endpoints are the duration and quality of survival, the probability of tumour response and toxicity due to treatment. Reliable assessment of the impact of the intervention on these endpoints requires careful attention to the design, conduct, analysis and reporting of the trial. Many investigators have provided important guidelines for protocol design and for selection of appropriate numbers of patients; for the procedures that are appropriate to define tumour response; and for statistical analysis and high quality reporting [1, 2]. Most cooperative oncology groups have initiated on-site reviews, which have concentrated on verifying tumour response by examining X-rays and other supporting data. They have also recorded protocol violations related primarily to patient eligibility or major deviations between dose and schedule specified in the protocol and those recorded in the patient's chart. In contrast, little attention has been paid to technical aspects of the administration of chemotherapy. The report of Dr Vantongelan *et al.* (p. 201) is a welcome addition to quality control: an EORTC venture to review the technical aspects of administration of chemotherapy in participating centres as well as details of the dose and schedule given to patients.

The outcome of patients whose cancers are treated by surgery or radiotherapy depends on the technical skill of the specialist. When quality control was applied retrospectively to radiotherapy given as part of combined modality treatment for small cell lung cancer in a large cooperative group trial, patients who received radiotherapy with major protocol violations had significantly worse survival [3]. Subsequently, the EORTC and the Radiation Therapy Oncology Group (RTOG) have implemented sophisticated mechanisms for assessing quality control for radiotherapy [4]. These programmes have highlighted the need for precise instructions on technique, prescription of volume and dose distribution, and the importance of reviewing radiotherapy portals by check films. The intervention of quality control has undoubtedly had a beneficial impact on quality of treatment, and this benefit is not restricted to patients in clinical trials.

Quality control of the delivery of chemotherapy is not often reported. However, there is considerable variability among institutions that contribute to cooperative group trials. An EORTC study reported in 1981 [5] showed that patient eligibility, protocol adherence and submission of data forms were far superior in institutions that contributed large numbers of patients to chemotherapy trials than in minor contributors, although the definition of protocol variation was not specified. These findings were not confirmed by an Eastern Cooperative Oncology Group (ECOG) study, which found no differences in quality of participation in clinical trials of community hospitals and larger centres or in outcome measures of the patients treated [6]. Differences in outcome measures have been observed, however, among different institutions contributing patients to other cooperative group studies. For example, the complete response rate among institutions entering a large number of patients into a Southwest Oncology Group (SWOG) study of combination chemotherapy for acute myelogenous leukaemia (AML) was 53%, whereas it was only 25% in institutions that entered a small number of patients [7]. This difference may have been due to the higher dose given in larger institutions, to factors which influenced selection of patients, or to unrecognised factors related to the administration of chemotherapy and quality of patient care. Received dose and dose intensity are undoubtedly important in determining patients' outcome [8], but additional subtle aspects related to the delivery of treatment and the quality of care may be equally important. How can quality control be applied to these aspects of practice?

The quality control procedure piloted by the EORTC, described by Dr Vantongelan and colleagues, is a two-stage method of a mailed questionnaire followed by an on-site visit to participating institutions. The questionnaire asks in detail about the preparation and administration of chemotherapy that exceeds considerably the inventory often used for quality control applied to pharmacies of North American institutions participating in trials of chemotherapy. The site visit then reviews a sample of hospital charts for patients on-study, checks the calculated dose and recorded schedule, and compares this with data on the case report forms that are submitted to the central Data Center. The chart is also checked for documentation of side-effects and performance status of the patients, as well as the more usual components of on-site review such as eligibility and documentation of tumour response.

Although the programme is in its infancy, with only 10 centres visited, striking variations have been noted between centres (all of them major contributors) in the administration of chemotherapy. The site reviews disclosed problems related to lack of systematic recording of timing and doses of chemotherapy and treatment-related toxicity; and the complex and variable nature of hospital files led to difficulty in extracting information. The investigators were unable to verify a significant proportion of data on case report forms (about 20%) because of lack of documentation. As a result, the investigators propose a checklist that summarises on a single form the most important aspects of delivery of chemotherapy and follow-up.

The early findings of this study raise concerns about the quality of results reported from cooperative group clinical trials. The site visits were to major contributors and the EORTC experience [5] suggests that problems may be greater in smaller institutions. Moreover, the questionnaire is itself an intervention, and some problems may have been addressed in the interval which preceded the subsequent on-site visit. Further

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analysis of the results of this venture should aim at assessing the potential impact on the conclusions of clinical trials, with worst-case and best-case scenarios for data that could not be checked against the hospital chart.

Is the quality control procedure cost effective? The estimated $800 cost for a single site visit is modest in view of the potential gain in quality control and education, especially if this occurs early during the trial. One interpretation of the study is the need for greater clinical trial support within the institutions visited, and the level of such support is not indicated. The EORTC has an enviable record of entering large numbers of patients on important clinical trials, with rather meagre resources, but lack of support for clinical trial nurses and data managers is a frequent complaint of EORTC investigators. A report from ECOG has suggested that extensive training programmes for those involved in clinical trials is a major component contributing to the high quality participation of their community hospitals [6]. The EORTC programme should be used to study the influence of clinical trial support staff on quality of administration of chemotherapy by comparing the performance of institutions with different levels of support, and/or with support staff that have different levels of training and education.

The quality control procedures initiated by EORTC are important and should improve the quality of participation in chemotherapy trials. Further analysis of the data is awaited, but consistent improvements in administration of chemotherapy and follow-up of patients with precise recording of data may require expansion of funding to increase the availability and education of data managers within the participating centres.

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Cancer Incidence Registration

IN A RECENT issue of this Journal, estimations of the burden of cancers of various forms in the European Community countries were presented [1] and were the subject of a commentary [2]. This analysis was based on national mortality rates, available from vital statistics schemes in many countries, combined with the information on cancer incidence available regarding several regions within countries. The latter data are available from population-based cancer registries which have been established in an increasing number of parts of the world. In this issue of the Journal there is the report from the Cancer Registry which has been established for several years in the Canton of Vaud in Switzerland (Levi *et al.*, p. 207).

Production of cancer incidence statistics is not a simple task but one which involves cooperation of cancer physicians and pathologists and hospital records staff to provide information regarding cases, and the product of the work of demographers to provide estimates of the population by age and sex in the region covered by the registration scheme. All this information has to be collected and coordinated by the staff of the cancer registry. The collected information has a variety of uses including the calculation of the cancer incidence rates in the region, to monitor time trends in cancer occurrence, to examine geographical aspects of cancer within their region and to calculate and monitor population-based survival rates. Further uses of the data extend to their value in the passive follow-up of cohorts with a particular exposure to monitor whether their cancer rates are elevated and their use to epidemiologists conducting case-control and other epidemiological studies. Knowledge of the numbers of patients being treated for cancer provides a better basis for resource planning than merely having information available regarding the numbers of deaths from the disease.

The data regarding Vaud have certain interesting features. The rates of certain cancers (e.g. testis in males and breast cancer in females) in the Canton are among the higher levels recorded in Europe with stomach cancer rates being among the lower rates [3]. The incidence rate of breast cancer is increasing overall while the high rate of testicular cancer has apparently remained unchanged in recent years. The authors also note that the incidence rates for tobacco-related neoplasms appear to be stabilising but note that those cancers whose rates are increasing are those whose aetiology is less well understood. These are interesting observations not only for those working in the field of cancer treatment and research in the Canton but also serve as a comparison for other populations with similar data available.

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