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Chemotherapy Administration and Data Collection in an EORTC Collaborative Group—Can we Trust the Results?

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As part of a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group, 15 centres took part in a programme to evaluate the quality of treatment delivered and data collected. The centres were visited and facilities for treatment and data management were reviewed. Source data in randomly selected patient hospital records were compared with information which had previously been completed on case record forms and returned to the EORTC Data Centre. The review included 71% of the patients entered into the study and 76% of the treatment cycles. Chemotherapy was prepared by nurses or clinicians in 58% and by pharmacists in 42% of the centres and was administered by specialist nurses in 67% of the hospitals. 8776 items were checked with source data. 3.4% were incorrect, 0.2% were missing and 30% could not be verified as correct (mainly related to the lack of recording of toxicity data in hospital records). The mean doses of chemotherapy delivered and treatment intervals were those stipulated in the protocol but 21% of the cycles were delayed for avoidable reasons. Several modifications to the procedures for running chemotherapy trials were suggested by this survey including the use of a systematic checklist for recording toxicity and chemotherapy administration and the development of quality assurance programmes in other collaborative groups and single centres to ensure that published results are credible.
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INTRODUCTION

THERE IS an increasing trend in Europe and North America to evaluate the results of treatment of a variety of malignancies in collaborative group studies. It is difficult enough for a trial co-ordinator to ensure good compliance with protocols and obtain satisfactory data in his/her own single centre, but controlling compliance in multiple centres, particularly with wide geographic spread where different languages may be used in hospital notes, is almost impossible. Results (in terms of response rate) from single centres and collaborative groups are known to differ, often widely, when apparently the same treatment is used for a similar patient population [1]. One explanation for this, often quoted in the literature, is differences of patient selection but it is likely that other factors result in some of the observed differences—particularly variations in the quality of compliance with protocol chemotherapy doses and schedules and quality of data acquisition. The National Cancer Institute (U.S.A.) and South West Oncology Group (SWOG) have reported some information on quality control in multicentre trails [2, 3], but to date there has been no published detailed analysis of the quality of adherence to protocols (particularly relating to chemotherapy administration) for collaborative groups. In order to properly interpret the results of collaborative group studies and understand why their response rates are often lower than those for single centres, it is important to know whether contributing members are actually adhering closely to the protocols.

The EORTC Soft Tissue and Bone Sarcoma Group (STBSG) is a well-established cooperative group which comprises oncologists with considerable experience of treating patients in trials. All members work in specialist cancer centres. A study was established between this group (during one of its phase II trials) and the EORTC Quality Control Group to monitor the quality of chemotherapy administration and data acquisition and thereby to obtain information on the credibility of its results.

The trial chosen involved the treatment of patients with advanced soft tissue sarcomas. Only two chemotherapy agents regularly produce response rates of over 20%—ifosfamide and doxorubicin [4, 5]. The use of these agents in combination necessitates modification of dosage because of associated severe myelotoxicity [6]. With the availability of the haemopoietic growth factors, the STBSG initiated a study which utilised doxorubicin and ifosfamide in combination at optimal dosage (75 and 5 g/m^2, respectively) followed by subcutaneous injections of granulocyte–macrophage colony-stimulating factor (GM-CSF). The aim was to assess the feasibility of administering such a regime to determine whether it might form the basis of a future randomised Phase III study. Several problems were envisaged for such a study. Many institutions would contribute and the trial had to be performed to *Good Clinical Practice* (GCP) guidelines as GM-CSF was an investigational agent. Frequent biochemical and haematological investigations had to be performed at strict time points and extensive documentation of the results was necessary. This regimen of chemotherapy was new, and it was possible that GM-CSF would not allow these doses to be given safely. The rapid reporting of serious toxicity, and of side-effects of GM-CSF, had to be assured so that the trial could be closed immediately if necessary. This treatment would be

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palliative for the majority of patients and treatment-related deaths or severe toxicity could not be accepted. For these reasons, a high quality of data acquisition and reporting was necessary and a rapid flow of data through the EORTC Data Centre in Brussels would occur. This complex trial performed by a large cooperative group (involving 16 centres in five countries) was, therefore, an ideal model to use for monitoring the quality of adherence to protocol therapy and data collection. We now report the results of such a programme.

PATIENTS AND METHODS

Patients and treatment

Adult patients with metastatic progressive soft tissue sarcomas received chemotherapy with doxorubicin 75 mg/m^2 given as a short intravenous infusion and ifosfamide 5 g/m^2 (with mesna) given as a 24-h intravenous infusion. After the completion of ifosfamide, GM-CSF (Behringwerke) (250 μg/m^2/24 h) was given by daily subcutaneous injections at home either by the patient, a family member or by a visiting nurse for up to 14 days. Investigations included response assessments after alternate chemotherapy cycles, biochemical profiles every 3 weeks and full blood counts with differentials on six occasions between courses of treatment.

Quality control assessments

During the study, centres were assessed by members of the Quality Control Group. The responsible clinicians received a mailed questionnaire covering general technical aspects of drug preparation and administration. Information on procedures for prescribing, the personnel within the treatment team responsible for each stage of drug administration, local facilities for preparation of cytotoxic agents and the sources of drugs were included. Details on antiemetic policy and procedures for recording of information on case record forms (CRF) were included in the list (and were not specifically related to this particular protocol). A mutually agreeable date was then arranged for a site visit by two or more members of the team (one always being a clinician and the other usually a senior data manager from the EORTC Data Centre). The questionnaire was completed prior to the site visit and was discussed on arrival by the visiting team. Subsequently, information on CRF (which had been submitted to the Data Centre) was checked against source information in the patient hospital case notes (up to 7 patients randomly selected per centre). Items checked included all aspects of drug administration, biochemical and haematological values and variables relating to patient eligibility and toxicities of treatment. Detailed information on the questions asked has already been reported [7]. Where information was missing or could not be verified from source material, appropriate coding on a specially designed form was completed [7].

As part of the visit, facilities in the hospital were reviewed. These included the pharmacy, ward, outpatient department and data management offices (when present). Following a site visit, all data was transferred to one member of the Quality Control Group for analysis. Each centre was assigned an anonymous code number.

RESULTS

A total of 16 centres entered 111 patients into this trial. Fifteen centres were visited for this programme in four countries. The one centre which was not visited had entered only 1 patient into the trial. The case records of 78 patients were examined. This represented 71% of the total patient population. 8776 items of information which had been entered onto the CRF were checked against source data in hospital notes.

General evaluation report

The self-completed questionnaries sent to responsible physicians prior to a site visit provided information on the arrangement of chemotherapy services within the centres. Cytotoxic drug reconstitution was always performed in laminar flow cabinets and protective clothing was provided. Chemotherapy was prepared by pharmacists in six centres, by nurses in seven centres and by physicians in two centres. In one centre, three separate individuals checked that the correct dosage was drawn-up and reconstituted but in two centres there were no checks on a single individual who prepared the cytotoxic drugs. The remaining centres had systems which involved two separate individuals checking that the correct doses were prepared. The median interval between chemotherapy preparation and administration was 60 min (range 2 min–30 h). In all instances doses were rounded up to the nearest easily measurable value rather than rounded down. All centres had similar antiemetic policies which utilised a steroid (almost always dexamethasone) with either metoclopramide or a $5HT_3$ antagonist. Specialist nurses administered the chemotherapy in 10 centres and physicians in the remaining five.

Quality of adherence to protocol chemotherapy

An essential aspect of this trial was that chemotherapy should be given at full protocol dose intensity. The doses and timings of administered chemotherapy were checked against prescription charts and nursing records. The mean doses of doxorubicin and ifosfamide given over all courses were 102% (range 94–110) and 102.5% (range 89–107), respectively, of the planned protocol doses. The mean dose of GM-CSF given was 100% of that required but the range was greater (14–114%) reflecting the fact that this was usually self-administered by the patient at home and instructions were sometimes incorrectly interpreted.

Although the overall median interval between chemotherapy courses was as required by the protocol (21 days), delays of up to 34 days occurred on 65 cycles (30% of the courses analysed). When treatment delays were documented they were found to be due to organisational problems in 66% of instances. Local clinicians had always been unaware of such problems prior to the site visit and subsequently altered their practice for arranging repeat admissions. Toxicity (29%) and patient request (5%) were the other reasons for delays.

Data quality

Table 1 shows a breakdown of the centres visited, the number of patients reviewed and the percentages of incorrect data or data which could not be verified in each site. The amount of data which was missing from CRF was small (<1% in all centres), and the percentage of data which was incorrectly entered was generally acceptable (<3% in 9 centres). However, in six centres the amount of incorrect data varied between 4 and 7.5% and in the majority of instances this related to the incorrect transposition of drug dosages. Other information which was most commonly incorrectly transcribed was patient performance status which had not been clearly documented in the case notes and was incorrectly interpreted by the data manager.

A major problem in some centres was the high percentage of data which had been entered onto CRF which could not be verified from source information in the patient case notes (Table 1). This mainly related to the toxicities of treatment which were

Table 1. Data quality in individual centres

Centre code	Number patients	Number of variables checked	% data incorrect	% data verified from files
621	7	752	3	98
622	7	694	3	81
623	6	603	2	98
624	7	838	3	55
625	5	680	3	83
626	5	515	3	81
627	7	686	3	48
628	3	357	5.3	89
629	4	367	4.5	80
630	3	384	6.2	81
631	5	651	1	43
632	6	606	7.5	57
633	2	288	6	59
634	6	724	4	57
635	5	671	3	43

often entered onto the CRF (in 53% of instances with a gap >1 month since treatment) by data managers who had never seen the patients and who assumed that if a toxicity was not recorded in the case notes, it had not occurred.

An encouraging aspect of this study was the high percentage of required data (predominantly laboratory variables) which were collected as required by the protocol. All centres obtained over 50% of the variables which were required and in the majority of instances all the necessary information had been collected.

Interesting variations in the way that CRF were completed were observed. In all but two countries full time professional data managers were employed. In those centres without data manager support, clinicians completed the forms with a resultant clear increase in the percentage of incorrect data being entered on the forms (Table 2).

DISCUSSION

The results of clinical studies investigating treatment options in any disease may have a major impact on the way that patients are subsequently managed. It is, therefore, essential that the results obtained are a correct reflection of the efficacy of the therapy. There are many potential sources of error during the course of a trial that may lead to a publication which overestimates or, equally importantly, underestimates the value of a treatment. Overestimates can result from selection of patients with favourable prognostic variables and incorrect interpretation of results (unfortunately sometimes due to the prevailing pressure to publish only positive data). Among the causes for underestimating a treatment may be failure to administer drugs correctly and misinterpretation of responses.

Table 2. Data quality control and professional data managers

Data managers	Number of centres	% incorrect data mean (range)
Employed	10	2.7 (1–4.5)
Not employed	5	5.8 (4–7.5)

Cancer patients are a particularly vulnerable group who will frequently seek any therapy which is offered. Chemotherapy, when used, may only provide palliation and modest improvements in survival in many instances and has the potential for life-threatening toxicity. It is thus important that such patients are treated in carefully designed protocols. Significant advances in treatment can only be made if the results are analysed as part of a clinical trial, and in order to detect potentially valuable therapies or rapidly reject ineffective regimens these must be performed to the highest standards.

Two important aspects of chemotherapy trials have a major bearing on the quality of the information that is obtained—how closely the treatment described actually correlates with the therapy delivered and how closely the parameters recorded in a data base and used to analyse the study relate to the information in the patient case records. Surprisingly, there is little information available from the literature on data quality control [2, 3, 7] and even less on the quality of adherence to protocol therapy in different institutions participating in multicentre trials. Possibly of more concern is the lack of information on quality of therapy and data in single institutions where one individual can publish information which has not been audited in any way. Despite several decades of clinical trials in cancer medicine, this is the first large systematic investigation performed (involving a detailed review of over 70% of all patients entered into a study) to obtain information on quality control of both treatment and data.

A major reason for the paucity of information on quality control is that site visits are time consuming and expensive. Even though all centres were highly motivated in this study and cooperated fully, each visit required a minimum of half a day of work for all involved, plus at least a further half day of travelling (often with the need for an overnight stay). There was, therefore, a substantial cost involving lost salaries, hotel and transport fares. Travelling expenses alone averaged 652ECU ($US 797) per centre visited. Significant additional time was necessary for subsequent data handling. A thorough quality control programme consequently requires adequate funding and dedicated personnel—particularly if it involves multiple institutions—and this must be considered before such a programme is established.

The first information collected related to the facilities within each centre. Variables which could contribute to the quality of the results included the level of training of prescribing clinicians, organisation of pharmacies and personnel preparing chemotherapy, methods for checking doses, provision of specialist nurses to administer therapy, and methods of recording data. All patients were treated either in specialist cancer hospitals or in oncology units within university hospitals and, in the majority of instances, prescribing of drugs was supervised by senior experienced medical oncologists. Facilities provided for reconstitution of cytotoxic agents were satisfactory with the provision of protective environments and rapid transfer of chemotherapy to the bedside for administration. Standardised antiemetic policies were established in all hospitals. Perhaps surprisingly, drugs were often prepared on the ward by nursing staff rather than in a central pharmacy. An important mechanism for ensuring that major errors in prescribing are not made is that the personnel prescribing chemotherapy are different from those reconstituting it. A potential method for improving the service in these centres could be the provision of oncology pharmacies with specialist staff familiar with the protocol who can detect any errors made by clinical staff. In every instance that major errors of administration of doses of cytotoxics occurred, the drugs

were not reconstituted in a specialist pharmacy. During the preparation of chemotherapy a mechanism should exist to check that the correct amount of drug has been dispensed. In all centres but two there was at least one separate individual who provided such a safeguard.

The inclusion of specialist nurses should be regarded as essential in any oncology department. Not only do they give support and advice to the patients, but they also have the training to administer chemotherapy safely and to provide another important check on the correct prescribing of drugs within protocols. In many institutions they provide continuity of care while junior medical staff, who rarely have the time to become familiar with all the ongoing protocols, rotate to other departments. Only 10 of the 15 centres contributing to this study employed trained oncology nurses to routinely give chemotherapy. An increased awareness of the importance of specialist oncology-trained nurses should be encouraged in this group.

An important aspect of chemotherapy trials is that there should be close adherence to administration of full protocol dose-intensity of all cytotoxic agents [8]. Information on treatment prescribing was obtained in this survey. Clinicians in every centre were obviously aware of the importance of dose, all rounding-up prescribed doses rather than compromising on the amount given with each cycle. In the rare instances that the dose administered was below that stipulated in the protocol, the cause was always a mathematical error of calculation. The other aspect of dose-intensity—the time interval between courses—was not adhered to so closely. Treatment delays were avoidable (not due to toxicity) in 21% of cycles and the major reason was incorrect readmission dates being given to patients by administrative personnel. The detection of such problems, which had not been apparent to the investigators, has led to alterations of organisation in the involved centres and will result in improvements in protocol adherence in future studies. It will also allow the study co-ordinator to interpret the results of the trial correctly—the treatment delays had previously been interpreted as due to a failure of GM-CSF to allow administration of full protocol dose intensity in these patients.

The quality of data entered onto CRF was carefully monitored with 8776 items being checked. The amount of missing information was $<1\%$ in all centres and would appear to be an acceptable figure which was identical to that obtained previously [7]. The amount of data which was incorrect when compared with source information was $<3\%$ in nine of the centres and again this figure is regarded as acceptable by members of the group. However, the finding that $>6\%$ of the data was incorrect in three of the centres should be regarded as unacceptable. An important finding was that information was more frequently incorrect in centres without professional data managers. A strong case can be made for funding data managers in institutions which are performing complex phase II trials. There is little point in spending large sums of money on treating patients with expensive drugs and arranging large numbers of investigations if the recording of data is subsequently performed to a low standard. Unfortunately, organised programmes of training and accreditation in data management are not available in some European countries and this problem is currently being addressed by the EORTC.

A problem highlighted by this programme was the difficulty of obtaining information from hospital records. There was no standardised format for recording data and a large amount of time was taken searching for drug charts and laboratory results. Of particular concern was the high percentage of data entered on the CRF which could not be verified from source information in several centres. This mainly related to toxicity assessments and clearly in a trial of a therapy for which the main aim is palliation of symptoms, correct and thorough reporting of toxicity is essential. As a result, a systematic checklist for toxicity assessment was developed during this programme and has been described in detail elsewhere [7]. When data on toxicity had been coded, this was often in excess of 1 month after the patient had been seen and the reliability of such information must be questioned. In all new studies of the Soft Tissue Sarcoma Group a standard toxicity assessment chart (which includes a record of drug administration) will be used and included in the patients' notes.

Several other important aspects of this study were noted. Laboratory values and other data which had arrived after completion of the CRF was often obtained at the site and increased the amount of information which will be available for the analysis of this trial. Responses could be reviewed and verified. Problems with interpretation of variables in the CRF could be discussed and centres made aware of deficiencies or strengths which they had. An encouraging aspect of this programme was the anxiety and defensiveness of those visited. All were clearly concerned to provide high quality data and were distressed by deficiencies in their centres when these were highlighted. This should ensure that future data will be of a higher standard and is clearly important with the increasing strictures being imposed on investigative centres by the guidelines of *Good Clinical Practice*.

The information derived from this quality control assessment allows several conclusions to be drawn. The centres participating in the study are among the best academic departments of medical oncology in Europe and should be expected to perform clinical trials to a high standard. For the majority of patients each course of treatment was given at the correct dose intensity with adequate safety checks on prescribing and with the availability of well-trained medical and nursing staff. Despite this, avoidable mistakes were made and in particular unnecessary treatment delays occurred on a significant number of occasions. There was good adherence to the required schedule of investigations but the quality of recording of toxicity was unacceptable. Completion of CRF was performed to a high standard in the majority of centres but, when professional data managers were not employed, errors occurred at a frequency which cannot be accepted. Collaborative groups should insist on minimum standards which have to be met by centres for continued membership. These standards can only be realised if site visits are made as part of a quality assurance programme and deficiencies are detected when present. The results of the Sarcoma Group study, when published, will be more credible because both the treatment delivered and data obtained have been carefully scrutinised and this programme will continue in future trials.

It is hoped that quality control programmes will be extended to other collaborative groups and to single centres who perform trials using chemotherapy. If important problems can be detected in centres which are among the best oncology departments in Europe, deficiencies will certainly exist in others. Obviously the cost of visiting large numbers of centres and performing frequent detailed analyses for all trials in each would be prohibitive. A more practical approach would be the development of a systematic programme which aimed at occasional visits to all centres with a review of data and treatment quality for a small selection of patients entered into a particular trial. This should provide information which was applicable to

the running of all trials within the institute. The knowledge that a site visit could occur should encourage closer protocol adherence and better standards of data management. Such a programme can only improve the credibility of clinical trials. Its development could be hastened if peer-reviewed journals insisted that consideration of papers for publication be dependant on agreement by centres to a programme of random checks by an independent Quality Assurance Group. The most important result of such a development should be improved standards of care for patients with cancer.

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Indication and Limits of Megatherapy and Bone Marrow Transplantation in High-risk Neuroblastoma: A Single Centre Analysis of Prognostic Factors

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76 patients with high risk neuroblastoma were treated with one (41 patients) or two consecutive courses (35 patients) of megatherapy. Autologous bone marrow transplantation was scheduled after each megatherapy. Univariate analysis confirmed two prognostic factors in this heterogeneous study population: no bone lesions before megatherapy and age at diagnosis of less than 2 years with 5-year progression-free survival rates of 51% ($P < 0.0007$) and 53% ($P < 0.025$), respectively. Both factors were shown to be of independent prognostic significance using the Cox proportional hazard model. Identification of prognostic factors should help to define the interest and limits of megatherapy. We consider that elective megatherapy followed by innovative treatments appears justified in patients with persisting bone disease. In contrast, megatherapy has to be re-evaluated for patients showing a more favourable response pattern and/or young age, ideally in a randomised, prospective trial. *Eur J Cancer*, Vol. 29A, No. 7, pp. 947–956, 1993.

INTRODUCTION

NEUROBLASTOMA is the most common childhood solid tumour before the age of 5 with a prognosis closely related to disease extension and age at diagnosis. In 30% of the cases neuroblastoma presents as localised disease (stage 1, 2 and 3); the prognosis is generally good with survival rates ranging from 40 to 90% and is influenced by the degree of local disease extension and the quality of surgical excision [1–3]. In 5% of cases, neuroblastoma is observed in infants of less than 1 year of age with a very particular disease pattern (stage 4s); although these patients present with metastatic spread to liver, skin and bone marrow but without bone lesions, the survival is more than 80% at 5 years [4, 5]. In contrast, 65% of neuroblastomas present at diagnosis as high-risk stage 4 metastatic disease involving most frequently bone marrow and bones. Major efforts have been undertaken to improve their prognosis. Historical control groups had a survival expectancy of only 10% at 3 years with conventional multimodality treatments [6–8]. More intensive induction

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