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Original Paper

The Use of a Systemic Therapy Checklist Improves the Quality of Data Acquisition and Recording in Multicentre Trials. A Study of the EORTC Soft Tissue and Bone Sarcoma Group

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The aim of this study was to verify whether the introduction of a systemic therapy checklist in the performance of multinational multicentre studies improves the quality of data acquisition and recording. We retrospectively analysed the results obtained through the use of this checklist in a study of the EORTC Soft Tissue and Bone Sarcoma Group. During the clinical trial, data were recorded in the hospital record with optional use of a predesigned EORTC Systemic Therapy Checklist. After completion of the study, 11 centres were monitored for the use of this checklist. Monitors were highly experienced medical oncologists. Items checked included all aspects of patient eligibility, drug administration, biochemical and haematological values, variables related to toxicities of treatment and response parameters. Data of 183 cycles given to 51 patients were checked. A total of 8983 items were checked. 91% of the data was reported correctly, 1% was missing and 6% was reported on the case record from (CRF) but could not be retrieved in the hospital record file. Compared with data obtained before the introduction of the checklist (68% correct, 4% incorrect, 0.1% missing and 28% on CRF but not in hospital files), these results show marked improvement generally. In centres where no Systemic Therapy Checklist was used, 85.9% of data were correct 2.8% incorrect, 0.7% missing and 10.6% only on CRF, which compares unfavourably with those where the Systemic Checklist was completely used (97.7% correct, 0.7% incorrect, 1% missing, 0.6% only on CRF). In addition the time required for data checking largely decreased by the use of the checklist—without this, a median of 3.5 cycles could be checked per hour, whilst if the checklist was used, this number increased to 6.5 cycles per hour. The use of a Systemic Therapy Checklist as an integral part of the hospital file for data recording in multicentre multinational trials is highly recommended and leads to a major improvement in data quality. © **1997 Published by Elsevier Science Ltd.**

Key words: quality control, chemotherapy, cancer

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INTRODUCTION

INCREASINGLY THE results of large clinical studies are being implemented in the common practice of treating cancer patients. The question of whether the results of trials with selected patient populations can simply be projected to the common practice has frequently been addressed. However, this question becomes semantic if the appropriate conclusions cannot be drawn from studies due to the lack of trustworthiness of the data generated [1]. This means that various levels of quality control are of utmost importance in

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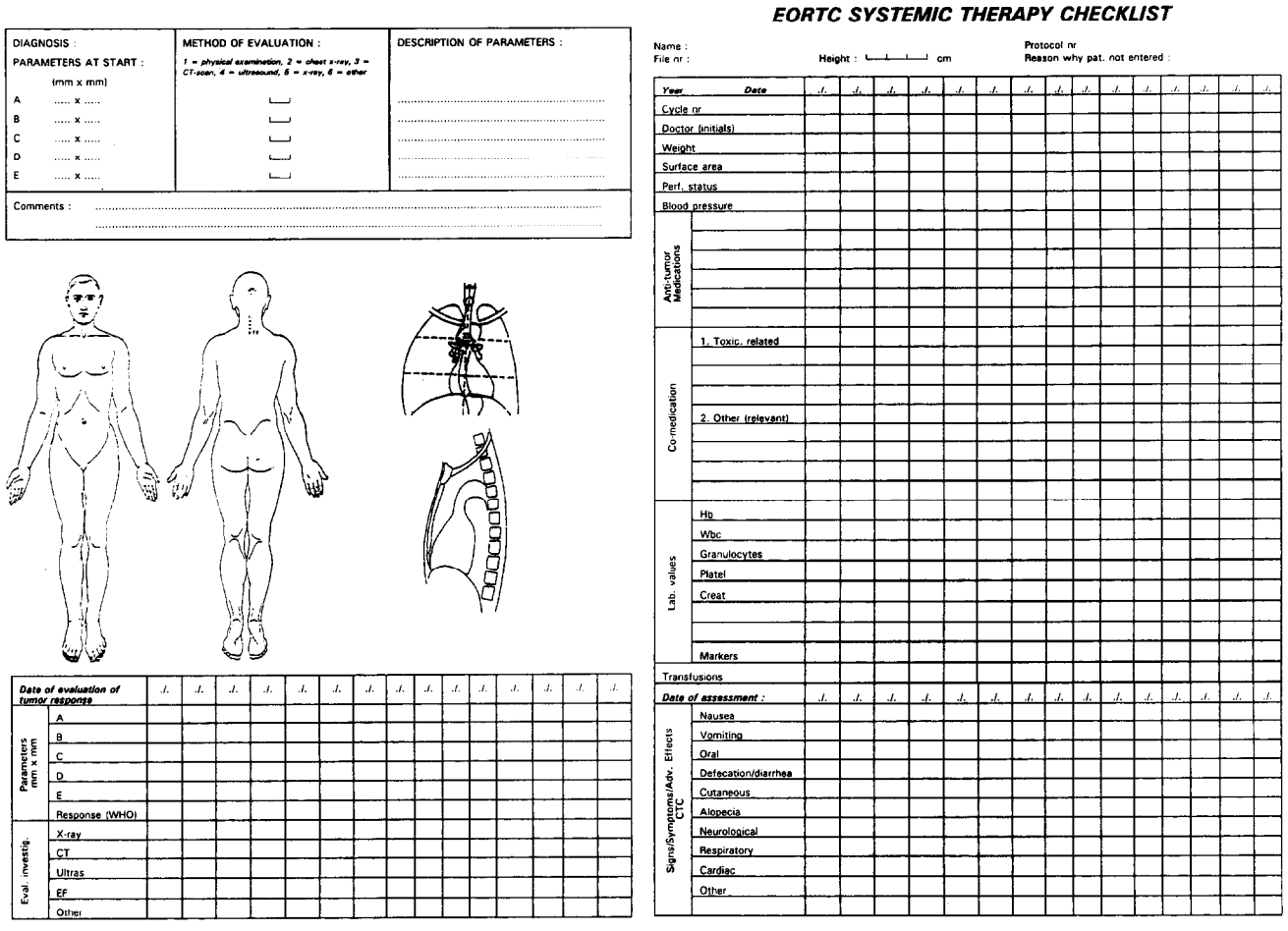

Figure 1. EORTC Systemic Chemotherapy Checklist.

the performance of any multicentre network, not only to ensure the appropriateness of the data generated, but also to enable a systematic comparison of the quality of the work in each centre [2], indicating centres that do not perform to the necessary standards. Previously, quality control studies concentrated on tumour response, and rarely on toxicity or treatment administration [3–5]. Within the complex structure of a large organisation, such as the European Organization on Research and Treatment of Cancer (EORTC), quality control has been an issue of priority since 1982 when the Radiotherapy Group started their quality control programme. In 1988 the EORTC Study Group on Data Management initiated a programme focused on data acquisition, mainly in chemotherapy trials [1]. Within this context the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) has previously actively participated [2], resulting in the set-up of a quality control system for chemotherapy trials within the group. In addition, in close collaboration with other groups, a systemic therapy checklist has been developed [2] and validated [6] to facilitate the recording of data and to improve their quality. The EORTC STBSG is a well-established co-operative group of oncologists with considerable experience of treating patients in trials. All members work in specialist centres, but nevertheless differences between centres exist and will always exist. To check whether the introduction of the systemic therapy checklist had resulted in a further improvement of the quality and retrievability of data recorded on the case record forms (CRF), the group decided to re-assess this issue, as previously assessed and published in 1991 [6].

The trial chosen involved a randomised study comparing standard doses of the combination of doxorubicin and ifosfamide with a higher dose of doxorubicin and the same dose of ifosfamide plus GM-CSF support (EORTC study protocol 62903). The trial had to be performed according to Good Clinical Practice (GCP) as GM-CSF was an investigational agent at the time the trial started.

PATIENTS AND METHODS

The clinical study protocol (EORTC 62903)

Adult patients with metastatic progressive soft tissue sarcomas were randomised to receive either doxorubicin at a dose of 50 mg/m^2 by i.v. bolus on day 1 and ifosfamide at a dose of 5 g/m^2 as a 24 h infusion on day 1 (with mesna), or the same dose of ifosfamide with doxorubicin at a dose of 75 mg/m^2 and GM-CSF (Behringwerke) 250 μg/m^2 s.c. once daily, days 3–17. Cycles were repeated every 3 weeks. Investigations included response assessment after alternative cycles, biochemical profiles every 3 weeks and full blood counts with differentials twice weekly. Side-effects were to be graded according to the Common Toxicity Criteria (CTC) of the NCI; responses had to be qualified according to standard WHO criteria. All responses are reviewed within the group and only accepted as a response if there is agreement between at least three reviewers.

Investigators were requested to use the EORTC systemic therapy checklist (Figure 1), or translations of the list, or similar lists approved by the quality control subcommittee of the group, to record the treatment data and results, as an integral part of the hospital file. At each 6-monthly meeting of the group, they were again encouraged to use this list and the importance of the retrievability of data was highlighted.

Chemotherapy quality and recording assessment

All 15 centres visited for the previous quality control assessment [6] were considered for a re-visit. Centres that had not actively participated, at the time of the present clinical trial, by accruing patients were excluded for the re-visit. For centres that had entered ≤5 patients in the present clinical trial, all patients were checked; for centres that had entered >5 patients, a random sample of 5 patients was taken by non-involved personnel of the EORTC data centre.

At the end of the study, the centres selected were visited by medical oncologists of the quality control subcommittee of the EORTC-STBSG. The site visitors were selected based upon their knowledge of the language of the country of the centre to be visited . The responsible physician in the visited institute received in advance information on which patient records were to be checked. The information on the case record form (CRF) (which had been submitted to the EORTC Data Centre) was checked against source information in the patient hospital record (up to a maximum of 6 cycles per patient). Items checked included all aspects of patient eligibility, drug administration, biochemical and haematological values, variables relating to toxicities of treatment, and response parameters. Detailed information on the questions has been published previously [1]. Evaluation of the quality of the data was coded as follows. The first code identified if the data was either 1. correct, 2. incorrect, 3. missing on the CRF or 4. present on the form but not retrievable in the hospital record. The second code identified the potential cause of the deviation identified by the first code either as: 1. incorrect transfer of information, 2. information missing in the hospital file or 3. related to unclear and /or ambiguous instructions on the study protocol and/or study forms. Third, data on the CRF not retrievable from the hospital record was encoded as either: 5. data directly coded on study forms by physicians without delay in filling forms, 6. data coded more than 1 month later by physicians or data managers and without available notes in the hospital record, or 7. data not available for other reasons which were than to be specified.

The site visitors also recorded the total time required to perform the site visit and whether or not the centre was using the EORTC systemic therapy checklist (or an approved alternative).

RESULTS

A total of 11 centres were visited and records of 51 patients checked (median per institute: 5, range: 2–5) for a total of 183 cycles (median per institute: 17, range: 3–22). This represents 58% of the centres participating in the clinical trial, 16% of all 314 patients entered and 14% of the total of 1264 treatment cycles given. A total of 8983 items were checked (Table 1). In the baseline data 43 (6%) were not retrievable from the hospital record. This mainly involved tumour measurement data that were performed by qualified personnel, but not listed as an integral part of the hospital record in a few institutes. Clearly the formal non-retrievability does not imply that these data were incorrect. This can also be suggested from the fact that the final evaluation data (which included the response evaluation) were incorrect for <1%, which may in turn also reflect the importance of response review systems within co-operative groups, as used by the EORTC-STBSG over the 20 years of its existence. In the treatment data, 91% was found to be correct. Only 1% was missing and 6% could not be retrieved from the hospital record. Issues of importance were: for the chemotherapy dose, 99% of data were correct; for performance score, 12% of data were non-retrievable; additional medication data were correct in 96%; and laboratory data were correct in 98% and missing in only <2%, despite the fact that the protocol prescribed very frequent blood sampling. The results of the analysis on side-effects are given in Table 2. In total, 87% of these data were correct, 4% were incorrect, 1% were missing and 8% could not be retrieved from the hospital records. The number of incorrect or non-retrievable data on asthenia reflects the difficulty in appropriately assessing this side-effect. Oedema was not an expected side-effect of this treatment and in fact did not occur. The 22% non-retrievability is presumably related to this expectation. Abdominal pain has been reported for GM-CSF previously and the large percentage of non-retrievability is, therefore, a concern. The 12% of incorrect reporting of nausea could fully be attributed to sub-optimal use of the checklist by involved investigators. Clearly this side-effect is extremely difficult to grade for data managers without the availability of appropriate data.

If compared to the data obtained in a previous study [6] (Table 3), the present results appear to have markedly improved. The number of verifiable data has increased, and the number of truly incorrect data has decreased. For unexplained reasons, the number of missing data (equally distributed over the different items (Table 1)) is slightly higher than before.

Table 1. Results of data-check given per type of data

	Baseline data	Treatment data	Final evaluation	Total
Items checked	773	7961	249	8983
Correct	717 (93%)	7211 (91%)	228 (92%)	8156 (91%)
Incorrect	8 (1%)	154 (2%)	10 (4%)	172 (2%)
Missing	5 (1%)	97 (1%)	1 (<1%)	103 (1%)
Only on CRF*	43 (6%)	499 (6%)	10 (4%)	552 (6%)

*Data recorded on the CRF, not retrievable in the patient's hospital record.

*Table 2. Results for side-effect recording**

	Correct	Incorrect	Missing	Only in CRF†
Asthenia	71	15	14	
Fever	89	3	8	
Infection	87	4	8	<1
Oedema	78	<1	22	
Weight gain	96	8		
Weight loss	94	1	4	<1
Abdominal pain	71	1	27	<1
Anorexia	80	10	10	
Constipation	80	1	19	
Diarrhoea	89	1	10	
Nausea	78	12	10	
Stomatitis	87	<2	11	<1
Neurosensory	82	<1	17	
Neuromotor	82	<1	16	<1

*Numbers represent percentages.
†Data given on the CRF, but not retrievable from the hospital record.

Despite repeated requests as indicated, 5 centres did not use any checklist. In 2 of these, 94% and 99% of data were nevertheless correct. In both centres, only 1 physician was involved in the treatment of the patients on trial in that centre and with the checking of the case record forms. This suggests the importance of the feeling of involvement of investigators with studies in which they participate. In the other 3 centres, data were correct in 65%, 76% and 83%, incorrect in 6%, 3% and 6% and not verifiable in 26%, 21% and 10%, respectively. One centre used the checklist irregularly and had 84% correct data, 3% incorrect data and 12% non-verifiable data. The 5 centres using the checklist most of the time had a median of 95% correct data. In total, for items related to treatment, use of the checklist appeared to be related to the quality and retrievability of the data (Table 4).

The time required per cycle to check the CRF data with the source document decreased with an appropriate use of the checklist. 3.5 cycles/h (range 2.0–4.86) were checked when the checklist was not in use, 3.5 cycles/h (3.5–4.3) when partially used, and 6.5 cycles/h (6.29–6.66) if used completely.

DISCUSSION

The major difficulty limiting the effectiveness of quality control is the lack, in many centres, of systematic recording of timings and doses of chemotherapy administration and, in particular, treatment-related side-effects [1]. In addition, many hospital files are complicated and poorly organised,

Table 3. Comparison of results obtained prior to the introduction of a systemic therapy checklist with those obtained after its introduction

	1991 [6]	1995
Total no. of items checked	8776	8983
Correct (%)	68	91
Incorrect (%)	4	2
Missing (%)	0.1	1
Data on CRF not on file (%)	28	6

Table 4. Results given per use of the systemic therapy checklist

	Use of checklist			
Status of data	Not at all *n* (%)	Yes, partially *n* (%)	Yes, completely *n* (%)	Total *n*
Correct	3424 (86)	1746 (83)	2041 (98)	7211
Incorrect	111 (3)	29 (2)	14 (1)	154
Missing	28 (1)	48 (3)	21 (1.0)	97
Data on CRF, but not on file	422 (11)	64 (3)	13 (1.0)	499
Total	3985	1887	2089	7961

and the information is difficult to find [2]. For these reasons among others the EORTC has developed its systemic therapy checklist [2].

The present study was initiated to assess the value of the use of the EORTC Systemic Therapy Checklist for the quality and the verifiability of the generated data. In our opinion, the data do show that the use of such checklists is one of the factors to improve the quality of the data. The investigators involved in the visited centres were largely the same as for the previous assessment. In the instances where checklists were used, a high number of correct data was found, while in those cases were the checklist was not used, a large number of non-verifiable data was still found, apart from those centres with a highly committed investigator. Since increasingly large numbers of different physicians are involved in the treatment of cancer patients, it becomes difficult to rely on the involvement of all of them to ensure a high quality of data, and presumably related to this, patient care.

Previously it has frequently been suggested that the differences in the outcome between apparently similar trials could have been related to patient selection. Our results suggest that another factor may simply be a difference in the quality of data recording between centres. In our previous experience, we found a high percentage (2–57%) of data which had been entered on to the CRF and could not be verified from source information in the patient case notes [6]. However, the high percentage of laboratory data that was retrievable was encouraging [6]. The latter result was confirmed in the present study, while moreover the low percentages of the non-verifiable data, missing data and incorrect data suggest that the data are an appropriate reflection of reality. This means that data from a co-operative group using a checklist can be considered to be trustworthy [6]. Since most of the trials performed by co-operative groups are intended to study refinements in the day-to-day care of patients, their results should be and are used by physicians in the community for treating their own patients outside of clinical trials. This becomes even more important in view of recent publications indicating the survival of patients may be related to factors such as the experience of the treating team of physicians. In a recent study, Junor and associates showed that survival of ovarian cancer patients markedly improved when treatment was co-ordinated by a multidisciplinary team [7]. McArdle and associates [8] have published their results from a survey on colorectal cancer showing that surgeon experience is directly related to postoperative morbidity and survival. Finally, for breast cancer, in studies involving 3786 and 12861 patients, respectively, it was

shown that survival rates were higher for patients cared for by specialist surgeons [9] and that survival rates after chemotherapy and hormone therapy was also directly related to the experience of the treating physician [10]. Clearly data published from multicentre studies should not only be optimal, but should also be used. The use of a Systemic Therapy Checklist during the performance of multicentre study might be of help in optimising data reporting.

In conclusion, the systemic therapy checklist facilitates recording of data, serves as a reminder for the treating physician and improves the quality of generated data. It helps to shorten the duration of site visits that are a necessity in clinical trials.

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