A prospective monitoring of fatal serious adverse events (SAEs) in a Dutch Colorectal Cancer Group (DCCG) phase III trial (CAIRO) in patients with advanced colorectal cancer

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Background: Early and correct assessment of treatment-related mortality is highly important in clinical cancer trials. However, no data are available on the quality of safety monitoring.

Patients and methods: An on-site review was carried out by the study coordinators of the individual charts of all patients participating in the Capecitabine-Irinotecan-Oxaliplatin (CAIRO) study who had died within 30 days of the last administration of study drugs when death was accompanied by any other event than disease progression. The relationship between treatment and death was categorized as unrelated, remote, possible, or probable and submitted to an independent data monitoring committee (IDMC). These results were then compared with the initial assessment of the local investigator.

Results: Forty of 820 patients qualified for review. The relationship between cause of death and study drugs was changed in 26 patients (65%). A major protocol violation (MPV) was identified in 12 of 14 patients with a probable relationship between cause of death and study treatment.

Conclusions: There was little agreement between the relation as assessed by the local investigator compared with the IDMC. A quality control improves the assessment of safety results and the observed MPVs underscore the importance of educating medical staff and patients.

Key words: colorectal cancer, data management, monitoring, protocol violations, serious adverse events

introduction

An important aspect of clinical trials in cancer patients is an early and reliable assessment of the relationship between adverse events and treatment. For a timely update of this crucial information, serious adverse events (SAEs) have to be reported according to the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines. As defined by ICH-GCP, an SAE is any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH-GCP article 1.50). Most study protocols define a period during which SAEs have to be reported, and usually this is from the signing of the informed consent form until 30 days after the last administration of study drugs. This implies that in clinical trials all hospitalizations and deaths occurring within 30 days of last study drug administration have to be reported within 24 h. The SAE reports are centrally collected, assessed by the principal investigators (PIs), and/or study coordinators and finally submitted to an independent data monitoring committee (IDMC).

The IDMC consists of independent experts to assess intervals, the progress of a clinical trial, the safety data, and the critical efficacy end points and to recommend to the sponsor whether to continue, modify, or stop a trial (ICH-GCP article 1.25). Within this system, the early safety monitoring of clinical trials by the PIs and IDMC largely depends on the early and reliable assessment of SAE reports.

Although SAE reports are the most important way to monitor the early safety and to assess the treatment-related mortality, there is no information available about the quality of SAE reporting by the local investigators. We carried out a quality control on the reporting of SAEs in a large prospective randomized phase III trial.

patients and methods

In the CAIRO study of the Dutch Colorectal Cancer Group [1, 2] registered with ClinicalTrials.gov with the number NCT00312000, 820 patients with advanced colorectal cancer (ACC) from 74 Dutch hospitals were
randomized between first-line capecitabine, second-line irinotecan, and third-line capecitabine + oxaliplatin (sequential treatment arm) versus first-line capecitabine + irinotecan and second-line capecitabine + oxaliplatin (combination treatment arm). Registration of patients was carried out by a telephone call or fax of the local investigator with the central data management office, which included a confirmation of all eligibility criteria. A protocol summary and checklist which summarized the eligibility criteria, treatment and evaluation schedule, and recommended dose modifications for the most frequently expected toxic effects was made available to all investigators for inclusion into the file of each participating patient. Furthermore, before the initiation of the study, three regional investigators’ meetings were organized to inform investigators and other research staff about the protocol. The protocol contained specific instructions for eligibility both for study entry as well as for the initiation of subsequent treatments. As a prospective part of the protocol, patients who had died within 30 days of the last administration of study drugs and whose death was accompanied by any other event than disease progression, irrespective of the causality reported for this event by the local investigator, were selected for this analysis. The study coordinators (MK and CJP) carried out an on-site review of the individual charts of these selected patients, and they assessed the relationship between treatment and death based on all available documentation. The relationship of the event to study treatment was categorized as unrelated, remote, possible, or probable as was also previously done by the local investigator on the SAE form. The results of the assessment by the study coordinators as well as the original SAE reports were submitted to the IDMC, who made the final assessment of causality.

results

study population

Of the 820 patients enrolled in the study, a total of 746 SAEs were reported in 443 patients. These SAE reports included 630 hospitalizations, 112 deaths occurring within 30 days of last administration of study drugs, and four other reasons. Of these 112 deaths, nine were reported ≤24 h, 42 were reported ≤2 weeks, and 70 were reported >2 weeks after the date of the event with a median time of reporting of 34 days (range 0–1261). In 72 of these 112 cases, disease progression was the obvious single reported cause of death. The remaining 40 patients were eligible for on-site review. The characteristics of these 40 patients did not differ from the overall study patient population except for age [median 68 years (range 52–79) versus 63 years (27–84), respectively, P < 0.01].

review results

Of the 40 patients whose charts were reviewed, the local investigators assessed the relationship between their death and the study medication as unrelated in 14, remote in six, possible in nine, and probable in 11 patients. The study coordinators assessed the deaths as unrelated in two, remote in 10, possible in 14, and probable in 14 (Table 1). The assessment by the study coordinators was confirmed by the IDMC in all cases. Compared with the assessment of the local investigators as documented on the original SAE reports, the relationship between cause of death and study drugs was changed by the review in 26 patients (65%). In 20 patients (50%), the study coordinators increased the level of causality, with in three patients the causality even being changed from unrelated to probable.

<table>
<thead>
<tr>
<th>Local investigator</th>
<th>IDMC</th>
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<tbody>
<tr>
<td>Unrelated</td>
<td>2</td>
</tr>
<tr>
<td>Remote</td>
<td>0</td>
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<td>Possible</td>
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<td>Probable</td>
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<td>Total</td>
<td>2</td>
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IDMC, independent data monitoring committee.

protocol violations

In the 14 patients whose death was established after review as probably related to study treatment, the causes of death were neutropenic sepsis (n = 8), neutropenic fever (n = 2), and dehydration due to diarrhea (n = 4) (Table 2). In 12 of these 14 patients, one or more major protocol violations (MPVs) were identified. These concerned the administration of chemotherapy despite an abnormal renal function (n = 1), the administration of irinotecan despite elevated serum bilirubin concentration (n = 2), continuation of capecitabine therapy despite previous or ongoing severe diarrhea (n = 7), and continuation of study drugs despite a decreased World Health Organization (WHO) performance status (PS) of three or more (n = 4). In five of these 12 patients, the MPVs had already been identified by the regular data management, and in seven, they were identified during the review. In addition to these MPVs, four patients were considered ineligible for study participation, which was not detected after standard data processing. The reasons for ineligibility were prior systemic treatment for ACC (n = 2), WHO PS of three and partial bowel obstruction (n = 1), and abnormal renal function at baseline plus severe leucopenia during prior adjuvant chemotherapy (n = 1).

discussion

To our knowledge this is the first randomized phase III trial in which the quality of the SAE reporting was prospectively assessed. For our review, 72 of the 112 SAEs reporting a death occurring within 30 days of the last administration of study drugs were excluded because the cause of death was disease progression and no other concomitant medical events were reported. Although we did make an effort to obtain additional information to confirm this, we acknowledge that this may have introduced a selection bias by which we underestimated the number of treatment-related deaths. However, the objective of our review was not a meticulous quantitative analysis, but a study to assess the quality of SAE reporting.

We recorded a disagreement between the assessment of the local investigators and the IDMC on the relationship between the study drugs and death in 65% of the patients whose charts were reviewed. Local investigators frequently underestimated the relation between the administration of study drugs and death. The CAIRO study tested the optimal use of well-established cytotoxics (capecitabine, irinotecan, and oxaliplatin), and all participating investigators had previous experience with the use of these drugs. However, insufficient
knowledge about the safety profiles and management of toxic effects cannot be excluded as a cause for the observed underestimation. Another possibility is that the short reporting period of 24 h after the occurrence of the SAE may not always allow a full and comprehensive assessment of the SAE. We assume this underestimation is not limited to SAEs reporting death but applicable to the reporting of SAEs in general. However, this was not investigated.

Of concern is the fact that a MPV was involved in 12 of the 14 treatment-related deaths. The most frequently occurring MPV was the continuation of capecitabine despite the presence of diarrhea. The cause of death of two ineligible patients in this review was probably related to study treatment (patient 1 and patient 12 in Table 2). In both patients, the reason of ineligibility likely played a role in the observed toxicity leading to death. Another two patients were ineligible for second-line treatment with irinotecan because of an elevated serum bilirubin, and these patients subsequently died of febrile neutropenia. This underscores the importance of educating investigators and patients in order to prevent unnecessary severe toxicity and of checking all relevant data before randomization and initiation of treatment cycles. As described in the 'Patients and Methods' section, a protocol checklist containing the most relevant information on this subject was distributed to all investigators, but we have no information as to its use. Meetings were also organized to inform the investigators about the protocol. This is more than the average trial; therefore, we believe that the results do not reflect shortcomings in the study organization but a general problem in clinical trials.

The results of similar reviews have been published; however, these were only carried out in retrospect upon the occurrence of unexpected severe toxic effects. Examples in metastatic colorectal cancer studies are European Organization for Research and Treatment of Cancer (EORTC) study 40015 [3] and Intergroup study N9741 [4]. EORTC study 40015 [3] was closed after eight deaths unrelated to disease progression had occurred. The individual hospital files were inspected and discussed with the physician to determine whether the observed deaths were related to or exacerbated by the study treatment. Four deaths were considered as related, three as exacerbated, and one as unrelated to study treatment. In the Intergroup study N9741 [4], a panel of five independent medical oncologists reviewed the causes of the observed early deaths. Of the 23 observed deaths, 16 were assessed as treatment related after central independent review. Both reports did not present information on any initial discrepancy between the assessments of local investigators and study coordinators or independent panel or on the involvement of any MPV that could have attributed to treatment-related deaths. In this respect our results are unique, at least to our knowledge. We believe that such information provides relevant data, which contribute to an accurate interpretation of study results.

In conclusion, a quality control by on-site review of hospital charts of patients experiencing SAEs may improve the quality of the assessment of treatment-related mortality. This process revealed relevant and new information, such as MPVs and patient ineligibilities. This implies that the assessment by the local investigator may not reflect the true relationship between an SAE and the study medication and that routine data management may not reveal all relevant information. Our data should make investigators and data managers aware of these pitfalls. The implementation of novel information and
communication technologies may add to prevent protocol violations as described.

The implementation of planned reviews, as described here, as a routine part of clinical studies should lead to a better quality of reported data. The review of treatment-related mortality is being continued in subsequent CAIRO studies [5], and a quality control program has been initiated in which other aspects such as protocol adherence are investigated.

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references


