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Editorial Comment

Early mortality rates: a tool for phase III trials or for changing standard practice?

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Defining and describing (dose-related) side-effects of chemotherapy are among the aims of phase I and II oncology trials. Phase I studies are intended to assess the safety of a drug or regimen, phase II to confirm the feasibility and assess long-term safety. They are usually performed in a single or just a few institutions. Due to the novelty of the regimen and the fact that safety is considered a major concern, it is sometimes the case that patient selection in such trials is rather conservative.

If phase I and II trials are performed appropriately, the safety aspect should become less of a concern in phase III trials since investigators will know what to expect, how to manage the observed side-effects, and how to avoid entering patients that should not be entered in view of organ dysfunction, poor clinical condition and other factors. Nevertheless, since phase III studies have a different aim, and are mostly multi-centre, it is possible that the population becomes less well selected, whilst remaining within the limits of the protocol criteria.

Most of the time, phase I and II studies have indeed appropriately predicted side-effects and designed ways to manage them. Fortunately, exceptions are truly rare. However, that does not mean that such exceptions do not occur. Whether this means that "Early mortality detected in a clinical trial is one of the most important parameters for assessing the safety of chemotherapy regimes", as indicated by Katopodis and colleagues [1], in their paper in the current issue of European Journal of Cancer entitled "60-Day all-cause mortality rates in patients treated for gastrointestinal cancers, in randomised trials, at the Royal Marsden Hospital" is questionable. Is early mortality the hidden safety parameter we should be looking for like detectives?

Or is it that the investigators have been looking for a way to control something that should not happen? Surely it would be better not to have to look for early mortality rates as a primary safety endpoint in phase III trials. We do not mean to suggest that mortality should be ignored or not reported, we only wish to highlight the fact that the safety aspect of treatment should have been carefully assessed and reported before phase III studies are designed and initiated. Yet, admittedly, despite extensive phase II data, an North Central Cancer Treatment Group (NCCTG) phase III trial on colorectal cancer assessing various schedules of Irinotecan with Fluorouracil and Leucovorin detected excessive toxicity with 8–16% lethal events [2], and this was confirmed in a Cancer and Leukemia Group B (CALGB) adjuvant study [3] using the same drugs. Apparently the early clinical trials in this case were not predictive. Importantly, most lethal events occured during the first cycle of chemotherapy. To establish a reference matrix in gastrointestinal (GI) cancers, the investigators at the Royal Marsden Hospital therefore looked at 60-day all-cause mortality rates in patients entered into prospective phase III trials of gastrointestinal cancers, treated with chemotherapy, since this rate is a simple estimate applicable to completed and (real-time) ongoing trials.

Whilst this is a large series, there are some limitations that are inevitable and should be taken into account:

The observations span a 10-year period (1992–2001) and patient care has evolved over time with the introduction of many new possibilities for managing side-effects or disease-related symptoms.

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The investigators assessed 3 types of death: treatment-related death, disease-related death, and death related to cardiovascular causes, independent of treatment recieved.

They studied a total of 1720 patients, divided into 3 diseases: oesophageal or gastric cancer, pancreatic cancer and colorectal cancer. The age range was 26–86 years, 7% of patients received chemotherapy as adjuvant therapy, 16% of patients had a performance score (PS) of 2 and 2% a PS of 3. This is perhaps somewhat surprising given the relatively modest activity of chemotherapy in the selected diseases and the fact that PS is a well known prognostic factor for achieving response.

As usual in retrospective analysis (albeit the trials subjected to the retrospective analysis were performed prospectively), there is quite a variety of chemotherapy regimens involved, with considerable differences in the side-effects that would have been predicted from literature. For example, the trials included agents like Mitomycin C, which has well known, unpredictable and frequently severe side-effects balanced against minimal activity. Since the side-effects of treatment will vary by regimen, it is difficult to fully extrapolate the results to any given population.

Gender and age did not have a significant impact on 60-day mortality. Interestingly the cardiovascular disease-related 60-day mortality was low in all groups. This lends support to recent data that age may not be a discrimating factor in our decision models as to whether or not to use chemotherapy.

However, fully according to expectation, PS was significantly related to a 5–12-fold higher chance of mortality ($P = 0.04$ to <0.001). On average, patients with metastatic oesophageal or pancreatic cancer have a worse PS, even within the limits of 1 grade, than those with colorectal cancer, certainly those undergoing adjuvant therapy for colorectal cancer. This is also evident from the Tables the authors provide. The disease-related 60-day mortality increased from 3.3% in colorectal cancer, to 4.7–7.4% in oesophageal and gastric cancer and to 11.1% in pancreatic cancer. The latter can thus likely be explained by the fact that metastatic pancreatic cancer and poor PS are inter-related.

Whilst it is not unexpected that poor PS and disease can be inter-related and are the most important factors related to early death, the rates observed in oesophageal and gastric cancers and particularly in pancreatic cancer, are of concern. This can be balanced against the positive observation of a low death rate due to toxicity in this series, although again the rate was highest in patients with pancreatic cancer. Therefore, these data seem to lend further support to a somewhat restrictive policy towards the use of chemotherapy in these diseases, particularly in pancreatic cancer.

With the exception of adjuvant chemotherapy for colorectal cancer, the aim of the chemotherapy is either to prolong survival or provide relief of symptoms. Therefore, the side-effects from treatment(s) must always be carefully balanced against their potential benefit. PS is not only a prognostic factor for early mortality, it is also a well known prognostic factor for toxicity and/or response. Considering the data provided in the paper of Katopodis, where the low death rate due to toxicity indicates careful patient selection, as well as other data related to phase III randomised trials, gastrointestinal cancers patients with a PS 2 or higher might be excluded from receiving chemotherapy. This way, 60-day mortality data may not be needed to guide the early assessment of safety in phase III randomised trials.

Conflict of interest statement

None declared.

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