# Toxicity evaluation in cooperative oncology clinical trials.

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## Introduction

The applicability of oncology trial findings to clinical practise is determined by whether the trial participants are representative of the actual population of cancer patients receiving therapy and whether the patients are treated identically in both situations. Patients of advanced age and poor performance status, who are normally excluded from clinical trials, may be more harmful to chemotherapy treatments [1].

Despite the fact that colorectal tumours are more common in the elderly, oncology clinical trials have a tendency to reject them in favour of younger patients with fewer comorbidities and a better performance status. Clinical trial impacts, such as greater medical imaging frequency, more frequent follow-up visits, and more attention from clinical trial staff throughout therapy, may result in additional benefit for cancer patients enrolled in clinical trials. Despite these assumptions, a comprehensive review found that the data is insufficient to support the assertion that cancer patients who participate in clinical trials have better outcomes than those who do not. However, all of the studies in that review focused on efficacy outcomes including overall survival and response to treatment, with only a few mentioning harm.

Irinotecan-based chemotherapy regimens are commonly used in the treatment of metastatic colon cancer, and they have increased patients' median survival to 20 months. However, because irinotecan regimens are linked to high incidence of severe diarrhoea, this survival gain is not without risk. Despite the fact that the toxicity rates for folfiri [irinotecan, leucovorin, 5-fluorouracil (5fu)], if (bevacizumab, irinotecan, 5fu, leucovorin), xeliri (capecitabine, 3-weekly irinotecan), and irinotecan monotherapy are well documented in phase ii and iii clinical trials, The goal of this study was to see if the toxicity rates of chemotherapy in non-trial individuals are comparable to those reported in published clinical trials [2].

The incidence of irinotecan-based chemotherapeutic toxicity in the palliative treatment of patients with metastatic colorectal cancer was studied in a retrospective single-institution record review. Toxicity rates in actual practise were compared to those in the largest phase III clinical study for each regimen published to date. The incidence of diarrhoea grades 3 and 4 was the primary objective. Other grade 3 or 4 toxicities, hospital admissions for chemotherapy-related toxicity, dosage reductions or delays due to toxicity, chemotherapy termination due to toxicity, and chemotherapy-related mortality were also secondary outcomes. The National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0, was used to grade toxicity. If a toxicity grade was not explicitly mentioned in the patient's chart, the two physician investigators who abstracted the data calculated a grade based on the facts available in each document and the criteria previously specified. The rates of toxicity seen in patients treated at the JCC were compared to those seen in a clinical trial that used the same irinotecan regimen [3].

There were no significant changes in toxicity rates once non-trial participants who failed to meet the age and performance criteria in the comparable clinical trials were excluded. The rates of mucositis and vomiting of any grade in the non-trial population were much lower, whereas the rates of neutropenia of any grade and grades 3 and 4 neutropenia remained significantly higher than the rates reported in the clinical trial data. Several toxicities, such as vomiting of any grade in the FOLFIRI group and grades 3 and 4 neutropenia in the IFL group, were actually considerably lower in our non-trial patients. One possible explanation for these disparities is that toxicities are poorly documented in non-trial patients' chart notes compared to those in clinical trials. Because many comparisons were done and sample numbers were limited in some groups—particularly for IFL, which is currently rarely used in clinical practise, and for XELIRI, which is a relatively new regimen—some of the much lower toxicity rates could be due to chance. In terms of age, it is generally established that patients enrolled in clinical trials are younger than non-trial patients and also younger than the general population of cancer patients [4]. Age differences are theoretically significant since drugs have different pharmacokinetics in the elderly, who have reduced renal and liver function, less total body water, and more fatty tissue.

Furthermore, aged persons are often believed to have several comorbid diseases, inadequate socioeconomic support, and diminished cognitive, all of which could restrict the potential benefit of systemic cancer therapy. Despite these theoretical dangers, we found no significant increase in the incidence of grades 3 and 4 toxicity in non-trial individuals above the age of 70. Several investigations have demonstrated that irinotecan regimens are well tolerated in fit older patients, confirming our findings. As a result, the current broad view is that chemotherapy can be used to treat elderly individuals who are fit enough to participate in clinical trials. When faced with pressures, frail elderly individuals are more likely to have negative results, and they should not get systemic chemotherapy. Unfortunately, the data to support or oppose the use of chemotherapy in the majority of older patients with an intermediate performance status is limited due to the

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underrepresentation of elderly patients in cancer clinical trials [5].

The current study has a number of flaws. We were unable to demand careful documentation of toxicities for non-trial patients due to the retrospective design, which may have resulted in underestimating of toxicity rates. We attempted to adapt the data for clinical trial inclusion criteria, but only age and performance status were taken into account. The four comparator trials utilised a variety of exclusion criteria that differed from one to the next, making it impossible to account for those criteria in the non-trial population.

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