Exclusion of Gastrointestinal Cancer Patients With Prior Cancer From Clinical Trials: Is This Justified?

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Abstract

Eligibility criteria for clinical trials are important for maintaining patient safety and scientifically valid results. Patients are commonly excluded from trials due to a history of a previous cancer. We demonstrate that patients with a previous cancer have similar survival to those who do not, and that this is not a justifiable reason to exclude them from clinical trial participation.

Background: Strict eligibility criteria are necessary to maintain patient safety and scientific validity in clinical trials. However, this may lead to impaired generalizability of results. As survival in gastrointestinal (GI) cancer relates mainly to the GI malignancy, we hypothesized that previous cancers do not impact on survival and are not a rational exclusion criterion. **Materials and Methods:** Patients treated with chemotherapy for a GI cancer in 2006 were identified from the electronic patient record at the Royal Marsden Hospital, London. Chart review was performed and patient age, gender, GI cancer stage, prior cancer stage, clinical trial availability/eligibility, and dates of cancer recurrence, death, and last follow-up were collated. **Results:** A total of 697 patients were identified. Fifty-four patients (8%) had a prior cancer; commonly breast (26%), prostate (17%), or colon (9%); most were stage I (42%) or II (37%). Two hundred ninety-seven (65%) patients had GI cancer recurrence, 7 (12%) patients had relapse of a prior cancer. Five hundred four (72%) patients have died, 170 (24%) are alive with no cancer, and 23 (3%) patients are alive with cancer. A total of 476 (94%) died of GI cancer, 2 (0.3%) of their prior cancer. Of all patients, 489 (70%) had an available trial, but 30% of patients with a prior cancer were ineligible for this reason. Overall and GI–cancer-specific survival were comparable for patients with/without a prior cancer. **Conclusions:** Survival for patients with a GI cancer requiring chemotherapy relates to the GI cancer and rarely a prior cancer. These patients should not be excluded from clinical trial participation.

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Introduction

Randomized clinical trials are the backbone upon which novel, increasingly effective therapies for cancer are based, and patient participation in randomized trials may lead to enhanced survival in particular in the short term.[1,2] However, the relevance of any clinical trial relies heavily on external validity, and trial generalizability may be significantly affected by factors such as exclusion criteria.[3] Furthermore, although results from clinical trials provide the empirical evidence used to treat patients rationally, patient accrual often falls short of expectations. This is demonstrated by a study of 114 Medical Research Council sponsored trials that revealed that less than one-third achieved their target enrolment within the specified timeframe.[4] Such low accrual rates may lead to insufficient statistical power and early trial termination. This

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represents a missed opportunity to answer a clinical and scientific question and a squandering of scant resources.

In theory, stringent eligibility criteria are necessary for clinical trials in order to maintain the safety of the patient and the scientific value of the protocol. Many of these criteria are common to all clinical trials, and along with "poor performance status," one of the most frequent of these is the exclusion of patients with any previous invasive cancer.[5,6] As the population ages and treatments of early stage tumors improve the proportion of patients with a prior history of cancer will inevitably increase — in 1971 there were 3 million cancer survivors in the United States; by 2007, this was 11.7 million.[7] Excluding these patients may further decrease the pool of potential clinical trial participants and may limit the generalizability of trials that are performed. Although many suggestions have been made as to how to increase participation in clinical trials, the validity of this commonly used exclusion criteria has not been previously examined.

As survival for patients with advanced gastrointestinal (GI) cancers (esophagogastric, pancreatic, hepatocellular, cholangiocarcinoma, and colorectal cancer) is more likely to be determined by that cancer that any previous cancer, we hypothesized that previously treated, unrelated cancers are less likely to impact on survival than is suggested, and that, therefore, a history of a previously treated cancer may not be rational reason to exclude patients from clinical trials in GI malignancies.[8-12] In this study, we examine the survival outcomes of patients with and without a prior cancer treated with chemotherapy in the GI Unit of the Royal Marsden Hospital over a 1-year period, and how a history of a previous cancer in a patient affected clinical trial eligibility during that timeframe.

Materials and Methods

For this retrospective observational study, we collected data on patients with GI cancer (colorectal, esophagogastric, pancreatic, and hepatocellular cancer) who received treatment between January 1, 2006, and December 31, 2006, at the Royal Marsden Hospital, London. Patient details were extracted from the electronic patient record. Eligibility criteria included age of 18 years and over, diagnosis of colorectal, gastroesophageal, pancreatic, or hepatocellular cancer, and treatment with chemotherapy in the year 2006. The following information was collected following chart review: patient age, gender, GI cancer stage, prior cancer tissue of origin and stage, clinical trial availability and eligibility, and dates of cancer recurrence, death, cause of death, and last follow-up. The electronic records of the Gastrointestinal Clinical Trials Unit were reviewed to identify the opening and closing dates of pertinent clinical trials for the period under review, and the relevant protocols were reviewed with respect to eligibility criteria.

All non-trial patients in the Gastrointestinal Oncology Unit are followed according to departmental protocols. Patients receiving active treatment for metastatic disease are followed as per chemotherapy protocol while receiving chemotherapy and 3-monthly while on treatment breaks. Patients with resected neoadjuvantly or adjuvantly treated cancers are followed every 3 months for the first year, then 6-monthly for years 2 and 3 following resection, and then annually until year 5 when they are discharged. Patients with resected stage IV colorectal cancer are followed for 7 years. Survival outcomes are collected by hospital administrative staff from a national database. Patients participating in clinical trials were followed as per individual trial protocol.

Overall survival (OS) was calculated from date of diagnosis of GI cancer to date of death and GI—cancer-specific survival (GCSS) was calculated from date of diagnosis of GI cancer to date of death where cause of death was GI cancer (censored at date of death for other cause of death). Survival estimates were calculated according to the Kaplan-Meier method, and are presented with 95% confidence intervals (CIs). Differences in survival between groups were compared with the log-rank test. All analysis was performed in SPSS version 22. Multivariate Cox regression analysis was performed using the variables age, stage, and cancer subtype in order to assess the independent impact of these variables on GCSS and OS. The study was reviewed and approved by the Institutional Review Board (SE61) and did not require patient consent, nor did it have any influence on patient management. The year 2006 was chosen to allow for adequate follow up of at least 5 years for surviving patients and mature assessment of survival data.

Results

Patient Population

A total of 697 patients were identified. Patient characteristics are presented in Table 1. The majority of patients were male (59%); the median age was 62 years for all patients. The most commonly treated GI tumor type was colorectal cancer (74%). Fifty-four (8%) patients had a previously treated cancer. Breast, prostate, and colon cancer together accounted for more than half of these previous cancers; almost 80% of previously treated cancers were Stage I or II. The median time from diagnosis of a previous cancer until current diagnosis was 7.9 years. Patients with a prior cancer were significantly older than patients without (median, 61 years vs. 67 years; $P < .001$), but were similar in all other baseline characteristics.

Of the 459 patients in the study with GI cancer that did not have metastatic cancer at presentation, 297 (65%) developed a recurrence of their GI cancer. Of the 54 patients with a previously treated cancer, 7 (12%) developed a recurrence of the previously treated cancer (however, 5 of these recurrences had occurred prior to their GI cancer diagnosis and been treated successfully with curative intent). Two patients had a recurrence of a previous cancer after their GI cancer diagnosis. These was 1 patient with a previous spinal cord glioma and 1 patient with a history of resected bladder cancer, and both of these patients died of their recurrent original non-GI cancer. To date, 504 (72%) patients have died, 170 (24%) are alive with no cancer, and 23 (3%) patients remain alive with cancer. Among the deceased patients, their primary GI cancer was the cause of death in 476 (94%) patients, followed by other reasons in 26 (5%) patients and their prior cancer in 2 (< 1%) patients.

Impact of Prior Cancer on Clinical Trial Recruitment

Of the 697 patients who were treated in the referent time period, 489 (70%) patients had an available clinical trial at the time of GI cancer treatment, and 113 (23% of patients with trial available; 16% of all patients) were enrolled into a clinical trial. Nine (2% of total) patients with a trial available were excluded because of a prior history of cancer. Of the 30 patients with prior cancer for whom a clinical trial was identified, 9 of these (30%) patients were excluded