SPECIAL ARTICLE

Mortality Associated With Irinotecan Plus Bolus Fluorouracil/Leucovorin: Summary Findings of an Independent Panel

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Purpose: To review and assign attribution for the causes of early deaths on two National Cancer Institute-sponsored cooperative group studies involving irinotecan and bolus fluorouracil (5-FU) and leucovorin (IFL).

Patients and Methods: The inpatient, outpatient, and research records of patients treated on Cancer and Leukemia Group B protocol C89803 and on North Center Cancer Treatment Group protocol N9741 were reviewed by a panel of five medical oncologists not directly involved with either study. Each death was categorized as treatment-induced, treatment-exacerbated, or treatment-unrelated.

Results: The records of 44 patients who experienced early deaths on C89803 (21 patients) or N9741 (23 patients) were reviewed. Patients treated with irinotecan plus bolus 5-FU/leucovorin had a three-fold higher rate of treatment-induced or treatment-exacerbated death than patients treated on the other arm(s) of the respective studies. For C89803, these rates were 2.5% (16 of 635) for IFL versus 0.8% (five of 628) for bolus weekly 5-FU and leucovorin. For N9741, these rates were 3.5% (10 of 289) for IFL, 1.1% (three of 277) for oxaliplatin plus bolus and infusional 5-FU and leucovorin, and 1.1% (three of 275) for oxaliplatin plus irinotecan. Multiple gastrointestinal toxicities that often occurred together were characterized into a gastrointestinal syndrome. Sudden, unexpected thromboembolic events were characterized as a vascular syndrome. The majority of deaths in both studies were attributable to one or both of these syndromes.

Conclusion: Close clinical monitoring, early recognition of toxicities and toxicity syndromes, aggressive therapeutic intervention, and withholding therapy in the presence of unresolved drug-related toxicities is recommended for patients receiving IFL or other intensive chemotherapy regimens.

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IN 1999, THE RESULTS of two large, randomized studies were reported that indicated that the addition of irinotecan (CPT-11; Camptosar, Pharmacia Corp, Peapack, NJ) to fluorouracil (5-FU) and leucovorin improved survival in patients with advanced-stage colorectal cancer.[1,2] These data led to the supplemental approval of irinotecan in March 2000 for use in first-line therapy for patients with metastatic colorectal cancer. It is estimated that 60% to 70% of patients with metastatic colorectal cancer receive irinotecan, fluorouracil, and leucovorin (IFL) as first-line chemotherapy in the United States.

In October 1998, the North Central Cancer Treatment Group (NCCTG) opened N9741, a phase III intergroup trial that compared several investigational combination chemotherapy regimens with 5-FU and leucovorin (daily × 5 days, Mayo Clinic schedule) in patients with metastatic colorectal cancer. The study was amended in March 2000 to terminate two experimental arms that were associated with unexpectedly high death rates and also to terminate the 5-FU plus leucovorin control arm.[3] The trial was revised into a three-arm study with IFL, administered in the fashion described by Saltz et al,[1] which became the new control arm. By the Spring of 2001, 841 of a planned 1,125 patients had been enrolled onto the three remaining arms of N9741: 289 treated with IFL, 277 treated with oxaliplatin plus bolus and infusional 5-FU plus leucovorin,[4] and 275 treated with oxaliplatin plus irinotecan on a once-every-3-weeks regimen.[5]

In April 1999, the Cancer and Leukemia Group B (CALGB) opened C89803, a phase III intergroup trial that compared IFL, administered as described by Saltz et al,[1] against 5-FU and leucovorin (weekly × 6 weeks, followed by a 2-week rest, Roswell Park schedule)[6] as adjuvant therapy in patients with Dukes' stage C (tumor-node-metastasis system stage III) colon cancer. By the Spring of 2001, the initial accrual goal of this study had been reached.

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A total of 1,263 patients were enrolled onto C89803: 635 treated with IFL and 628 treated with 5-FU and leucovorin by the Roswell Park weekly schedule.

On April 24, 2001, the NCCTG External Data Monitoring Committee identified an unexpected number of deaths that occurred within the first 60 days of study entry onto protocol N9741. In addition, it seemed that there were a disproportionate number of deaths that occurred in patients treated on the IFL control arm of the study. There were 14 deaths (4.8%) in 289 patients treated on the IFL arm; five deaths (1.8%) in 277 patients treated with the oxaliplatin, 5-FU, and leucovorin regimen; and five deaths (1.8%) in 275 patients treated with the oxaliplatin plus irinotecan regimen.[3,7] To place these results in proper context, the treatment-related death rate in the original study that evaluated irinotecan plus bolus 5-FU and leucovorin was reported as 0.9% (two deaths in 225 patients)[1] and the toxic death rates in other recent phase III trials were similar to this, ranging from 0.2% to 1.3%.[8,9]

These findings prompted a CALGB internal review of the early death rate in C89803. This review identified 19 deaths within the first 60 days of treatment: 14 (2.2%) of 635 patients treated with IFL and five (0.8%) of 628 patients treated with 5-FU and leucovorin.[7] To place these results in context, the death rate for patients treated on other recently reported colon cancer adjuvant studies ranged from 0% to 0.8%.[10,11]

After a series of conference calls in April 2001, the NCCTG suspended accrual onto N9741 on April 25, 2001, and the CALGB permanently closed accrual to C89803 on April 27, 2001. In addition to halting accrual, representatives of CALGB, NCCTG, Pharmacia, and the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) agreed that an independent review panel should be convened to review the medical records of the patients who experienced early death on both studies. This article summarizes the findings of that review panel.

The charge to the committee was to assign attribution for each death; to review the management of each patient with respect to protocol eligibility, chemotherapy administration, and adherence to dose-modification guidelines; and to identify a risk profile that might allow prospective identification of patients at high risk for early death.

PATIENTS AND METHODS

Data Retrieval

Between June and July, 2001, Theradex staff members visited each site at which an early death of a patient occurred on either N9741 or C89803. The records of one patient who died within 60 days of randomization were not reviewed because the patient was removed from study before the initiation of protocol treatment. At the request of the cooperative groups, one patient who died on day 62 of protocol treatment on N9741 and one patient who died on day 82 of protocol treatment on C89803 were included in this analysis because of concerns that these deaths were treatment-related. Therefore, this review was conducted from the records of 23 patients from N9741 and 21 patients from C89803.

Copies were made of all inpatient and outpatient treatment records as well as research records. All patient identifiers were deleted from the copies of the records made available to the reviewers. All patients were identified only by the unique numbers assigned by the respective cooperative group.

Data Abstraction

Theradex staff members abstracted critical data on each patient to assist in this review. This abstraction consisted of an eligibility summary, a summary of results of prestudy evaluations, a listing of prestudy and concomitant medication administered to each patient and categorized by known interactions with cytochrome p450 isozyme 3A4, and a chronologic summary of the clinical course that included drug dosages, dates of administration, adverse events, and medical interventions from the time of treatment initiation to the time of patient death.

Panel Review

This review was conducted in Princeton, NJ from July 13-15, 2001, by a panel of five medical oncologists not directly involved in either of the two studies. Copies of the entire inpatient and outpatient medical records of each patient were reviewed. Where available, autopsy reports were included in the patient record. Each patient record was independently reviewed in detail by one primary and one or two secondary reviewers. Each case was then discussed by the group to reach a consensus on the cause of death.

Criteria for Attribution of Cause of Death

In preparation for this review, the panel inquired about guidelines for attribution of death of a patient while on a clinical trial. The panel was informed that no such guidelines existed within the two involved cooperative groups, the Cancer Therapy Evaluation Program of the NCI, the Food and Drug Administration, or the Office for Human Research Protections of the Department of Health and Human Services. The existing system describes deaths on study as being treatment-related or treatment-unrelated, with qualifiers of none, unlikely, possible, probably, or definite used to convey the degree of certainty for the cause of death. The panel felt that this approach yielded so many different categories as to not be clinically useful. It was recognized that this system was most deficient in determining the cause of death in situations in which multiple adverse events occurred simultaneously. The inability of this system to identify the relative contributions of the therapy, the disease, and any underlying medical conditions to the patient's demise prompted the panel to consider an alternative method for death attribution.

The panel developed and used the following categories in an attempt to provide a more useful and clearer perspective on the cause of deaths on study. These definitions were developed in advance of the meeting and applied prospectively in the review of these records.

- Treatment-induced: Death clearly caused by protocol treatment.
- Treatment-unrelated: Death clearly unrelated to protocol treatment.

Table 1. Causes of Early Deaths on C89803

Treatment Arm	Total Deaths		Treatment-Induced Deaths		Treatment-Exacerbated Deaths		Treatment-Unrelated Deaths (no.)
	No.	%	No.	%	No.	%	
Irinotecan + bolus 5-FU/ leucovorin	16/635	2.5*	15/635	2.4	1/635	0.2	0
Roswell Park 5-FU/leucovorin	5/628	0.8	5/628	0.8	0		0
Total	21		20		1		0

NOTE. No. of patients/total no. patients treated with therapy.
*Includes one patient who died on day 82 of the study.

- Treatment-exacerbated: Death caused by exacerbation of an underlying medical disorder by protocol treatment. The medical disorder had to be pre-existing at the time of initiation of treatment. The patient's death would not have been expected in that time frame from the underlying condition had protocol treatment not been administered.

Limitations of Review

With three exceptions, as noted above, this review was limited to those patients who died within 60 days of initiation of protocol treatment. Because this analysis did not include patients who experienced severe but nonlethal toxicities or those who developed moderate, mild, or no toxicities, we could not create a risk profile for those patients most likely to encounter varying degrees of toxicity or die while receiving treatment. Our conclusions are, therefore, descriptive and rely solely on the observations made from the subset of patients who experienced early deaths on study.

RESULTS

Deaths in Each Treatment Arm and Attribution

CALGB 89803. Twenty patients died within 60 days of initiation of treatment. One additional patient who died on day 82 was added to this analysis at the request of the cooperative group. The causes of death, using the categories defined above, are listed in Table 1.

N9741. Twenty-three patients died within 60 days of study registration. One patient who was registered but never treated is not included in this analysis. One patient who died on day 62 was added to this analysis at the request of the cooperative group. The causes of death, using the categories defined above, are listed in Table 2.

There were triple the number of treatment-induced and treatment-exacerbated deaths on the IFL arms of each study compared with the other arms. Treatment-induced deaths were rarely because of any single toxicity. Deaths were most commonly the result of a cluster of toxicities that occurred simultaneously or in rapid succession. Summary tables that list the frequency and severity of individual toxicities but provide no information on the simultaneous occurrence of multiple toxicities do not adequately capture the full clinical impact of these episodes. Often, it was the combined effect of several moderate or severe toxicities that directly led to the patient's death.

Certain toxicities often occurred in association with other toxicities, especially in those patients treated with irinotecan plus bolus 5-FU and leucovorin. These concurrent or overlapping toxicities could be characterized into two syndromes.

Gastrointestinal Syndrome

This was defined as a constellation of gastrointestinal symptoms, including diarrhea, nausea, vomiting, anorexia, and abdominal cramping. Symptoms were often associated with severe dehydration, neutropenia, fever, and electrolyte abnormalities. Radiographic findings associated with this

Table 2. Causes of Early Deaths on N9741

Treatment Arm	Total Deaths		Treatment-Induced Deaths		Treatment-Exacerbated Deaths		Treatment-Unrelated Deaths	
	No.	%	No.	%	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	13/289	4.5	9/289	3.1	1/289	0.3	3/289	1.0
Oxaliplatin + bolus and infusional 5-FU/leucovorin	5/277	1.8*	2/277	0.7	1/277	0.4	2/277	0.7
Oxaliplatin + irinotecan	5/275	1.8	3/275	1.1	0		2/275	0.7
Total	23		14		2		7	

NOTE. No. of patients/total no. of patients treated with therapy.
*Includes one patient who died on day 62 of treatment and excludes one patient who was registered but never treated on study.

Table 3. Gastrointestinal and/or Vascular Syndromes as the Cause of Deaths on C89803

Treatment Arm	Treatment-Induced or Exacerbated Deaths		Gastrointestinal Syndrome–Induced or Exacerbated Deaths		Vascular Syndrome–Induced or Exacerbated Deaths		Deaths Due to Neither Syndrome	
	No.	%	No.	%	No.	%	No.	%
Irinotecan + bolus 5-FU/ leucovorin	16/635	2.5	12*/635	1.9	5*†/635	0.8	2/635	0.3
Roswell Park 5-FU/leucovorin	5/628	0.8	4/628	0.6	1‡/628	0.2	0	
Total	21		16		6		2	

NOTE. No. of patients/total no. of patients treated with therapy.

*Three patients experienced both syndromes and are therefore included in both columns.

†These vascular episodes were comprised of two myocardial infarctions, one pulmonary embolus, one cerebrovascular accident, and one pulmonary embolus or myocardial infarction.

‡This vascular episode was comprised of a myocardial infarction.

syndrome often included dilated bowel, air-fluid levels without anatomic obstruction, and thickened bowel wall.

Vascular Syndrome

This was defined as an acute, fatal myocardial infarction, pulmonary embolus, or cerebrovascular accident that occurred during or shortly after receiving chemotherapy. An underlying cardiovascular or thromboembolic condition may have been present, but if so it was stable or well-compensated at the time of initiation of treatment. The vascular event was not attributable solely to other treatment-induced toxicities (eg, severe dehydration) or other known causes (eg, immobility for a patient who develops a pulmonary embolus). The vascular syndrome may have occurred as an isolated event or in association with gastrointestinal or other drug-induced toxicities.

When these definitions were applied to the treatment-induced or treatment-exacerbated deaths described in Tables 1 and 2, they were frequently found to be associated with early mortality. These results are listed in Tables 3 and 4.

Time to Fatal Events

C89803. For those patients included in this analysis, the rapidity with which death occurred seemed to differ on the basis of treatment. For patients treated with the Roswell Park 5-FU and leucovorin regimen, the median time of death was day 47. For those patients treated with IFL, the median time of death was day 29. All 21 patients are included in this analysis because all deaths were either treatment-induced or treatment-exacerbated. Patients who died on the IFL arm of C89803 often had moderate to severe toxicities that resulted in dose attenuation but not treatment suspension prior to death. In contrast, patients who died on the Roswell Park arm of the study had few preceding toxicities and were treated on time and at full doses prior to the onset of fatal toxicities, which suggests a more acute onset of severe toxicity with weekly bolus 5-FU plus leucovorin than with IFL.

N9741. Differences in the interval between initiation of treatment and death are more difficult to assess on N9741 because some patients clearly died from cancer progression.

Table 4. Gastrointestinal and/or Vascular Syndromes as the Cause of Deaths on N9741

NCCTG 9741	Treatment-Induced or Exacerbated Deaths		Gastrointestinal Syndrome–Induced or Exacerbated Deaths		Vascular Syndrome–Induced or Exacerbated Deaths		Deaths Due to Neither Syndrome	
	No.	%	No.	%	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	10/289	3.5	6*/289	2.1	3*†/289	1.0	3/289	1.0
Oxaliplatin + bolus and infusional 5-FU/leucovorin	3/277	1.1	0		1/277	0.4	2/277	0.7
Oxaliplatin + irinotecan	3/275	1.1	1/275	0.4	0		2/275	0.7
Total	16		7		4		7	

NOTE. No. of patients/total no. of patients treated with therapy.

*Two patients experienced both syndromes and are, therefore, included in both columns.

†These vascular episodes were comprised of one myocardial infarction, one pulmonary embolus, and one cerebrovascular accident.

The median days of death for patients treated on each arm of N9741 were as follows: IFL, day 30; oxaliplatin + bolus and infusional 5-FU/leucovorin, day 30; and oxaliplatin + irinotecan, day 18. When this analysis was limited to the 16 patients who experienced treatment-related or treatment-exacerbated deaths, the median days of death were 28, 26, and 18, respectively. Although there does not seem to be any marked difference in the time to treatment-related death between groups when such patients are included or excluded from the analysis, it was noted that the median time to death in all three regimens was 30 days or less from the time of initiation of treatment.

Baseline Characteristics of Patients Who Died

The median age of patients who died in the control group of C89803 was 73 years, and the median age of patients who died in the IFL-treated group in C89803 was 69.5 years. These median ages are somewhat higher than the typical median ages of 60 to 63 years in patients enrolled onto cooperative group adjuvant colon cancer studies.[10,11]

The median ages of patients who died on each of the arms of N9741 were as follows: IFL group, 65 years; oxaliplatin + bolus and infusional 5-FU/leucovorin, 66 years; and oxaliplatin + irinotecan group, 68 years. However, when deaths that were considered to be treatment-unrelated are removed from this analysis, the ages tend to go up in all three groups. The median age of patients who died from treatment-induced or treatment-exacerbated causes on each of the arms of N9741 now became the following: IFL group, 69 years; oxaliplatin + bolus and infusional 5-FU/leucovorin, 66 years; and oxaliplatin + irinotecan, 69 years. These median ages also seemed to be somewhat higher, especially in the two irinotecan-containing arms, than the median ages of 61 and 62 years for patients enrolled onto the two prior phase III studies of IFL in patients with advanced-stage colorectal cancer.[1,2] Conclusions that can be drawn from these analyses are limited due to the unavailability of data on the ages of all patients treated on C89803 and N9741.

Location of the primary tumor (right-sided *v* left-sided) was also examined in this analysis. There did not seem to be a substantial difference in the representation of right-sided or left-sided primary tumors in patients who experienced early death on study.

Early deaths were observed in patients from all baseline performance status levels, Eastern Cooperative Oncology Group 0, 1, and 2. Although there did not seem to be a quantitative difference in the number of patients with any particular PS who experienced early death on study, it was recognized that the majority of patients enrolled onto these studies entered with PS of 0 or 1. An analysis of death rate by PS would be of interest to determine whether one group was at disproportionate risk for early death from any of these treatments. Concomitant medications, including known cytochrome p450 isozyme 3A4 substrates, inhibitors, and inducers did not have an obvious relationship with fatal events.

Patient Eligibility

Virtually all patients included in this review met eligibility criteria as outlined in the respective studies. The eligibility of one patient was questioned because of the lack of pathologic tissue from the presumed cecal primary, a pattern of serum tumor markers that suggested a primary tumor other than colon cancer (CA-125 was elevated out of proportion to carcinoembryonic antigen), and borderline performance status at the time of enrollment.

Treatment Administration and Adherence to Dose Modification Guideline

Isolated cases of dosing errors were noted, but no systematic problems were identified regarding adherence to protocol treatment or dose modification.

RECOMMENDATIONS

General

1. Improved criteria should be developed for attribution of cause of death that occurs in any patient who receives protocol treatment. One approach is proposed in which death is categorized as treatment-induced, treatment-unrelated, or treatment-exacerbated. This was the first time that these criteria were used, and they are open to critique and revision.

2. Real-time monitoring of life-threatening or fatal adverse events or hospitalizations can hasten identification of unexpectedly frequent or severe clinical toxicities in a multicenter trial and could enhance patient safety on clinical trials.[13]

Specific

1. Increased awareness is needed among health care providers regarding the described gastrointestinal and vascular syndromes associated with irinotecan plus bolus 5-FU and leucovorin treatment.

2. Patients treated with IFL should undergo weekly assessment, at least during the first cycle of treatment, by a clinician who is experienced in the use of this regimen and in the treatment of gastrointestinal cancer. This is especially important prior to weeks 3 and 4 of treatment, when most of the severe treatment-related toxicities that led to early death occurred. In general, more stringent guidelines are needed for

monitoring patients who are receiving IFL or any of the newer, more intensive combination chemotherapy regimens.

3. A more aggressive approach should be taken in the treatment of diarrhea that occurs in isolation or as part of the gastrointestinal syndrome with IFL. European investigators use the following approach: Patients are provided with a supply of loperamide and a prescription for an oral fluoroquinolone prior to the initiation of treatment. They are instructed that if delayed diarrhea occurs, they should begin taking loperamide 2 mg orally every 2 hours (4 mg orally every 4 hours at night) and continue until they are diarrhea-free for at least 12 hours. If the diarrhea persists for more than 24 hours despite loperamide, they should begin taking the oral fluoroquinolone and continue it for 7 days. If the diarrhea persists for longer than 48 hours, they should stop the loperamide and be hospitalized for parenteral hydration.[12] Oral fluoroquinolone treatment should also initiated in patients who develop an absolute neutrophil count (ANC) less than 500/μL, (even in the absence of fever or diarrhea) or a fever that occurs in the setting of diarrhea (even without neutropenia). Patients must undergo frequent clinical evaluation by a nurse or physician until resolution of the syndrome. Any decision regarding hospitalization should be based upon the patient's clinical status and the physician's ability to follow the patient closely as an outpatient.

4. Appropriate antibiotics should be initiated in any patient hospitalized with prolonged diarrhea, regardless of neutrophil count, and should be continued until resolution of diarrhea. Delayed initiation of antibiotics, premature discontinuation of antibiotics, or selection of inappropriate antibiotics occurred in a number of patients reviewed and is likely to have contributed to their deaths.

5. Physicians should consider grade and duration of toxicity, need and use of supportive care, impact on performance status, and interval since resolution of toxicity in the decision to administer a scheduled dose of IFL chemotherapy. To the extent possible, protocols should incorporate these elements in dose modification criteria.

6. Patients experiencing significant treatment-related diarrhea should not receive IFL chemotherapy. The toxicity should be considered resolved only if the patient has been diarrhea-free or restored to baseline bowel function for at least 24 hours without the use of antidiarrheals or antibiotics.

7. Abdominal cramping should be considered equivalent to diarrhea. If grade 2 abdominal cramping occurs, treatment should be halted until the cramping has fully resolved.

8. Blood tests should be obtained no more than 48 hours prior to scheduled treatment. Attention should be given to the trend of ANC. If it is falling rapidly, then the protocol should allow the physician to pause treatment even if the ANC is adequate for the patient to receive treatment.

9. Changes in electrolytes, including hyponatremia or hypernatremia, hypokalemia, and/or metabolic acidosis, may reflect early physiologic consequences of IFL-induced toxicity. Patients with perturbations in serum sodium, potassium, and/or bicarbonate, even without concomitant elevations in BUN or creatinine, should be carefully evaluated for dehydration and receive aggressive medical management, including fluid and electrolyte replacement.

10. Based on the experience in these and other colorectal cancer clinical trials, older individuals should be followed especially closely.

NOTE ADDED IN PROOF

Data available from the original trial reported by Douillard et al[2] in patients with advanced-stage disease and from ongoing adjuvant colon cancer studies (PETACC-3, E. Van Cutsem, personal communication) report treatment-associated death rates of well below 1% for irinotecan + infusional 5-FU and leucovorin regimens. The reasons for the apparent discrepancy between death rates in those studies and the CALGB and NCCTG studies, including drug administration schedule, should be evaluated further. This information should be considered in the design of future colon cancer adjuvant studies and when considering treatment options for patients with metastatic colorectal cancer who are not enrolled onto a clinical trial.

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APPENDIX

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