Neutropenic Colitis After Treatment of Acute Myelogenous Leukemia With Idarubicin and Cytosine Arabinoside

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• Objective: To determine the gastrointestinal toxic effects of idarubicin and cytosine arabinoside combination therapy in patients with newly diagnosed acute myelogenous leukemia (AML).
• Patients and Methods: We performed a single-institution retrospective analysis of the incidence of neutropenic colitis in patients with newly diagnosed AML receiving idarubicin and cytosine arabinoside combination therapy. Using pharmacy records, we identified 78 patients who received idarubicin during the study period of January 1997 to September 1998 and who agreed to a review of their medical records. Patients with preexisting bowel conditions were excluded from this analysis. We used a strict definition of neutropenic colitis that included clinical findings (severe abdominal pain, diarrhea, hematochezia, and/or peritoneal signs) plus radiographic evidence of bowel inflammation in the absence of an identified bacterial pathogen.
• Results: Of the 78 patients receiving idarubicin and cytosine arabinoside for treatment of AML, 65 were included in this study. We observed neutropenic colitis in 10 of these 65 AML patients. This complication was followed by sepsis in 3 patients and was the major cause of death in 4 of the 8 patients who died.
• Conclusion: This analysis suggests that neutropenic colitis is a frequent and serious complication of idarubicin and cytosine arabinoside treatment.

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AML = acute myelogenous leukemia; CT = computed tomography

During the past 30 years, sequential studies have expanded our knowledge of optimal induction therapy for acute myelogenous leukemia (AML). Currently, the combination of an anthracycline with cytosine arabinoside is the standard of care. The Cancer and Acute Leukemia Group B1 compared the relative efficacy and toxicity of daunorubicin at 30 or 45 mg/m² or doxorubicin at 30 mg/m² combined with continuous infusion cytosine arabinoside. Although there was no significant difference in the frequency or duration of complete remission, gastrointestinal toxic effects were more frequent in the doxorubicin group than in the daunorubicin group (13% vs 1%-4%).

Since this classic study, the anthracycline idarubicin has replaced daunorubicin as the anthracycline of choice in many centers. Four prospective randomized trials2-5 have compared daunorubicin with idarubicin. It appears that idarubicin has a superior complete remission rate, especially in young adults. The effect on overall survival is less clear because 2 of the studies suggested an advantage, whereas the other 2 did not. A recently published Eastern Cooperative Oncology Group6 study and a collaborative overview of 5 trials7 also failed to show a definite advantage of idarubicin over daunorubicin for older adults.

There is a paucity of data regarding the acute gastrointestinal toxic effects of the idarubicin and cytosine arabinoside combination. We report a retrospective analysis of the Mayo Clinic experience with regard to the gastrointestinal toxic effects of this regimen.

PATIENTS AND METHODS
Using pharmacy records, we identified 79 patients who received idarubicin during the study period January 1997 to September 1998. Only 1 of these patients denied review of medical records for research purposes. We then narrowed the analysis to include only those patients with newly diagnosed, previously untreated AML who received induction with idarubicin, a 12-mg/m² intravenous bolus injection, on days 1, 2, and 3 and cytosine arabinoside, a 100-mg/m² daily continuous intravenous infusion, for 7 days. Patients with residual disease apparent on bone marrow examination performed on days 12 to 14 were treated with a second cycle of the same drugs and schedule.

Patients receiving induction chemotherapy at our institution are treated in private rooms. There is no special air filtration, reverse isolation precaution, gut decontamination, or other prophylactic antibiotics. When patients become febrile, appropriate cultures are taken, and empiric broad-spectrum antibiotics are administered. This includes a third-generation cephalosporin with the addition of gram-positive aerobic coverage if the patient appears septic and metronidazole if gastrointestinal symptoms are present. Colony-stimulating factors are not used.
Patients were suspected of having neutropenic colitis on clinical grounds based on the occurrence of 3 or more of the following signs: fever, pronounced watery diarrhea (≥5 stools per day), abdominal distention and/or tenderness with rebound, bloody stools, or frank peritoneal signs. A diagnosis of neutropenic colitis also required (1) radiographic confirmation with findings of bowel wall edema involving 1 or more segments of the small bowel or colon; (2) multiple stool samples negative for ova, parasites, and Clostridium difficile toxin; and (3) stool bacteriologic cultures negative for enteric pathogens. Finally, to rule out the possibility that abdominal findings represented recurrence of previous bowel disorders, patients with preexisting bowel diseases, such as inflammatory bowel disease, diverticulitis, or ischemic colitis, were excluded from analysis.

RESULTS
Of the 78 patients receiving idarubicin and cytosine arabinoside during induction chemotherapy for AML between January 1997 and September 1998, 65 were included in the present analysis. The age range was 18 to 77 years, with a median age of 60 years. Thirty-five patients were male. The main reasons for exclusion of 13 patients were treatment in 8 patients and in 2 of 8 additional patients who required a second course of treatment because of residual disease on bone marrow examination performed on days 12 to 14.

Of the 65 patients who received idarubicin and cytosine arabinoside for newly diagnosed AML and did not have preexisting bowel conditions, 10 (15%) met the criteria for neutropenic colitis (95% confidence interval, 7.6%-26.5%). This complication occurred after 1 course of treatment in 8 patients and in 2 of 8 additional patients who were re-treated for residual disease on day 14. Six were men, and the median age was 62 years (range, 41-72 years). The median time of onset of symptoms was day 10 after the start of chemotherapy, but computed tomography (CT) confirmation was usually not obtained until day 14 or 15. At presentation of abdominal symptoms, all patients had absolute neutrophil counts of less than 0.5 × 10^9/L and were dependent on platelet and red blood cell transfusions.

Treatment consisted of complete bowel rest without suction, parenteral nutrition, and broad-spectrum aerobic and anaerobic coverage. Additional CT scans were performed as needed, primarily when perforation was suspected. It was not unusual to find residual bowel thickening for 14 or more days after the initial scan. No patient required immediate or delayed surgical intervention because of bowel perforation or other complications.

Of the 10 patients with neutropenic colitis, 3 developed positive blood cultures (Bacillus, Klebsiella, and Enterococcus species) a median of 10 days after the initiation of chemotherapy. Two of these patients survived the episode. Altogether, 4 of the 10 affected patients died during hospitalization (Table 1). The terminal event was multiorgan failure in 3 and presumed cardiac arrhythmia in 1 patient (who had requested that no resuscitation efforts be undertaken).

DISCUSSION
In the present study, we report that neutropenic colitis occurs frequently in AML patients undergoing induction therapy with idarubicin and cytosine arabinoside. The 15% incidence (10/65) is probably an underestimation of the extent of this complication because we used strict inclusion criteria, including radiographic confirmation. Common infectious origins, including C. difficile, were sought. If these were present, patients were thought not to have neutropenic colitis.

In addition, we excluded patients with preexisting bowel conditions to minimize the role of any comorbid conditions that might have predisposed or aggravated bowel inflammation. Although it would have been of interest to know if patients with preexisting bowel conditions were more likely to develop neutropenic colitis, the small number of such patients (1 with Crohn disease and 2 with ischemic colitis) precluded any meaningful analysis of this subset.

Two aspects of the clinical presentation of neutropenic colitis in this patient population merit comment. First, we found that no single clinical manifestation was observed in all patients. Second, in some patients the initial abdominal CT scan was normal, but florid bowel inflammation with edema and mesenteric streaking was observed when the study was repeated less than a week later. The delayed radiographic finding is reminiscent of similar delayed radiographic changes in neutropenic patients with pneumonia.

At present, it is unclear whether the high incidence of neutropenic colitis during induction therapy with idarubicin and cytosine arabinoside is unique to our institution or whether this complication has been previously unappreciated in other studies. In several prior trials using idarubicin, the total number of early deaths was reported rather than the specific cause, making comparison difficult. In a large Southeastern Cancer Study Group trial, 57% of patients undergoing induction therapy with idarubicin developed grade I-II and 16% developed grade III-IV diarrhea. It is possible that a significant proportion of the patients with severe diarrhea had neutropenic colitis, although this diagnosis was not specifically mentioned. It is also possible that the advent of more intensive chemotherapy, such as conditioning regimens for allogeneic or autologous transplantation,
has led to an underreporting of neutropenic colitis because clinicians are more willing to initiate intensive support, including bowel rest, parenteral nutrition, and broad-spectrum antibiotics, when abdominal symptoms develop.

Additionally, it is possible that we are highly sensitized to consider the diagnosis of neutropenic colitis because of the morbidity associated with the process. This might have introduced a bias in the ordering of confirmatory studies in a more systematic fashion.

It is unclear whether the neutropenic colitis observed in our patients represents a toxic effect of the idarubicin and cytosine arabinoside chemotherapy or an infectious disease caused by an undiagnosed pathogen. In either case, the diagnosis of neutropenic colitis was associated with considerable morbidity and mortality. Three of the 10 patients with neutropenic colitis in our series developed bacteremia, and 4 died during hospitalization of causes unrelated to refractory leukemia. In other series, neutropenic colitis has also been associated with a high incidence of septicemia (up to 65%) in patients with hematologic malignancies.10 This most likely reflects severe gut inflammation that provides a portal of entry for colonizing bacteria and assumes even greater importance with the emergence of increasing antibiotic resistance in these organisms. Further studies are needed to determine whether this complication can be diminished by altering antimicrobial treatment patterns or by a less dose-intensive regimen (eg, 8-10 mg/m² of idarubicin rather than the standard 12 mg/m² daily) in certain populations, such as elderly patients.

REFERENCES


Table 1. Demographics of Patients Who Developed Neutropenic Colitis After Induction Therapy for AML *

<table>
<thead>
<tr>
<th>Patient No./age (y)/sex</th>
<th>FAB subtype</th>
<th>No. of courses</th>
<th>Days from induction to death</th>
<th>Clinical course</th>
<th>Reason for death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/33/M</td>
<td>M6</td>
<td>1</td>
<td>42</td>
<td>Invasive Rhizopus pneumonia (BMBx results negative)</td>
<td>Neutropenic colitis, infection</td>
</tr>
<tr>
<td>2/41/M</td>
<td>M2</td>
<td>1</td>
<td>Lost to follow-up</td>
<td>Disseminated intravascular coagulation</td>
<td>NA</td>
</tr>
<tr>
<td>3/57/F</td>
<td>M1</td>
<td>1</td>
<td>Alive at 3 years</td>
<td>Bronchitis</td>
<td>NA</td>
</tr>
<tr>
<td>4/63/M</td>
<td>M0</td>
<td>1</td>
<td>473</td>
<td>Severe cervical spondylitis</td>
<td>Relapsed leukemia</td>
</tr>
<tr>
<td>5/68/F</td>
<td>M4</td>
<td>1</td>
<td>Relapsed at 94‡</td>
<td>Klebsiella bacteremia</td>
<td>Relapsed leukemia</td>
</tr>
<tr>
<td>6/68/M</td>
<td>M1</td>
<td>1</td>
<td>23</td>
<td>Blood cultures negative, day 14 BMBx not performed</td>
<td>Neutropenic colitis, ulcerative esophagitis</td>
</tr>
<tr>
<td>7/68/M</td>
<td>M2</td>
<td>1</td>
<td>69</td>
<td>Fungal endocarditis, small bowel infarction</td>
<td>Neutropenic colitis, infection, residual acute leukemia</td>
</tr>
<tr>
<td>8/73/M</td>
<td>M0</td>
<td>1</td>
<td>16</td>
<td>Bacillus bacteremia, BMBx results negative</td>
<td>Neutropenic colitis, sepsis</td>
</tr>
<tr>
<td>9/44/F</td>
<td>M4</td>
<td>2</td>
<td>294‡</td>
<td>Acute gastrointestinal bleed</td>
<td>Relapsed leukemia</td>
</tr>
<tr>
<td>10/55/F</td>
<td>M2</td>
<td>2</td>
<td>Relapsed at 365</td>
<td>VRE bacteremia, relapsed leukemia</td>
<td>Relapsed leukemia</td>
</tr>
</tbody>
</table>

*Patients 1, 6, 7, and 8 died during hospitalization for induction therapy. AML = acute myelogenous leukemia; BMBx = bone marrow examination; FAB = French-American-British classification; NA = not applicable; VRE = vancomycin-resistant Enterococcus. ‡M0 indicates unidentified acute leukemia; M1, acute myeloid leukemia minimal differentiation; M2, acute myeloid leukemia with differentiation; M4, acute myelomonocytic leukemia; M5, acute monocytic leukemia; and M6, erythroleukemia. †Patient had recovered from neutropenic colitis. Death related to disease.