Mortality in Overweight and Underweight Children With Acute Myeloid Leukemia

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ACH YEAR IN THE UNITED STATES, 500 to 600 individuals younger than 21 years develop acute myeloid leukemia (AML). Current treatment for AML typically consists of 3 or 4 courses of intensive, myelosuppressive chemotherapy with or without bone marrow transplantation from a histocompatible family donor. This therapy cures about half the children with AML; of the other half, most succumb to leukemia, but 5% to 15% die from toxic effects of treatment. Factors that predict treatment failure and death in AML are relatively older age and higher white blood cell (WBC) count at diagnosis, a slow response to the first course of chemotherapy, and absence of a histocompatible family member to donate marrow for transplantation.

Children’s Cancer Group (CCG)-2961 was a phase 3 international cooperative group trial for previously untreated AML. Thirty patients without out-of-protocol leukemia, or treatment-related mortality were excluded from the study. The trial accrued 902 patients with de novo AML. Thirty patients without outcome data and 104 infants younger than 1 year were excluded from this analysis, leaving 768 patients. AML was classified according to French-American-British criteria. Morphology, histochemistry, and karyotype.

RESULTS Eighty-four of 768 patients (10.9%) were underweight and 114 (14.8%) were overweight. After adjustment for potentially confounding variables of age, race, leukocyte count, cytogenetics, and bone marrow transplantation, compared with middleweight patients, underweight patients were less likely to survive (HR, 1.85; 95% confidence interval [CI], 1.19-2.87; P=.006) and more likely to experience treatment-related mortality (HR, 2.66; 95% CI, 1.38-5.11; P=.003). Similarly, overweight patients were less likely to survive (HR, 1.88; 95% CI, 1.25-2.83; P=.002) and more likely to have treatment-related mortality (HR, 3.49; 95% CI, 1.99-6.10; P<.001) than middleweight patients. Infections incurred during the first 2 courses of chemotherapy caused most treatment-related deaths.

CONCLUSION Treatment-related complications significantly reduce survival in overweight and underweight children with AML.

METHODS CCG-2961 opened on August 30, 1996, and closed on December 4, 2002. Patients from birth through age 20 years were enrolled after institutional review board approval of each participating institution and written informed consent. Patients with Down syndrome, Fanconi anemia, acute promyelocytic leukemia, acute undifferentiated leukemia, or treatment-related AML were excluded from the study. The trial accrued 902 patients with de novo AML. Thirty patients without outcome data and 104 infants younger than 1 year were excluded from this analysis, leaving 768 patients. AML was classified according to French-American-British criteria. Morphology, histochemistry, and karyotype.

Context Current treatment for acute myeloid leukemia (AML) in children cures about half the patients. Of the other half, most succumb to leukemia, but 5% to 15% die of treatment-related complications. Overweight children with AML seem to experience excess life-threatening and fatal toxicity. Nothing is known about how weight affects outcomes in pediatric AML.

Objective To compare survival rates in children with AML who at diagnosis are underweight (body mass index [BMI] ≤10th percentile), overweight (BMI ≥95th percentile), or middleweight (BMI = 11th-94th percentiles).

Design, Setting, and Participants Retrospective review of BMI and survival in 768 children and young adults aged 1 to 20 years enrolled in Children’s Cancer Group-2961, an international cooperative group phase 3 trial for previously untreated AML conducted August 30, 1996, through December 4, 2002. Data were collected through January 9, 2004, with a median follow-up of 31 months (range, 0-78 months).

Main Outcome Measures Hazard ratios (HRs) for survival and treatment-related mortality.

Results Eighty-four of 768 patients (10.9%) were underweight and 114 (14.8%) were overweight. After adjustment for potentially confounding variables of age, race, leukocyte count, cytogenetics, and bone marrow transplantation, compared with middleweight patients, underweight patients were less likely to survive (HR, 1.85; 95% confidence interval [CI], 1.19-2.87; P=.006) and more likely to experience treatment-related mortality (HR, 2.66; 95% CI, 1.38-5.11; P=.003). Similarly, overweight patients were less likely to survive (HR, 1.88; 95% CI, 1.25-2.83; P=.002) and more likely to have treatment-related mortality (HR, 3.49; 95% CI, 1.99-6.10; P<.001) than middleweight patients. Infections incurred during the first 2 courses of chemotherapy caused most treatment-related deaths.

Conclusion Treatment-related complications significantly reduce survival in overweight and underweight children with AML.

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type were centrally reviewed as described.\textsuperscript{10,11} Cytogenetic subsets were classified as normal, favorable [t(8; 21); t(9;11) or (inv 16)], unfavorable [del(7) or 7q-], or standard.\textsuperscript{3,5,6}

**Figure 1** illustrates the treatment plan for CCG-2961. Course 1 consisted of idarubicin, dexamethasone, cytarabine, thioguanine, and etoposide on days 0 to 3 and daunorubicin plus the last 4 drugs on days 10 to 13. Patients in complete or partial remission were randomized to course 2 therapy. Complete remission was defined as less than 5% marrow blasts, with recovery of neutrophils to greater than 1000 × 10\(^9\)/L and platelets to greater than 50000 × 10\(^3\)/µL, and partial remission was defined as 5% to less than 30% marrow blasts. Course 2 consisted of a repetition of induction therapy (regimen A) or fludarabine, idarubicin, and cytarabine (regimen B).\textsuperscript{12} After course 2, patients in complete remission and with a histocompatible relative able to donate marrow were assigned to marrow transplantation; those without donors were assigned high-dose cytarabine/L-asparaginase chemotherapy.\textsuperscript{4} Patients in remission after course 3 chemotherapy were randomized to standard follow-up or to interleukin 2.\textsuperscript{11} All patients received central nervous system prophylaxis with 8 doses of intrathecal cytarabine. Granulocyte colony-stimulating factor was given on day 14 ± 1 of courses 1 and 2 and continued until the absolute neutrophil count (ANC) was at least 1000 × 10\(^9\)/L.\textsuperscript{13} All systemic chemotherapy was given in the hospital.

Data entered onto study forms were abstracted from the medical record. They included age, sex, ethnicity, height and weight before each phase of therapy, doses of chemotherapeutic agents, toxicities, infectious complications, duration of hospitalization, and time to neutrophil recovery to 500 × 10\(^9\)/L and 1000 × 10\(^9\)/L. Treating physicians or nurses classified the individual’s race and ethnicity. Drug dosing was based on weight in kilograms up to age 3 years and by surface area thereafter. Dose modifications were provided for hyperbilirubinemia and after May 2001 for reduced glomerular filtration or creatinine clearance. There were no dose modifications for underweight or overweight patients.

Body mass index at diagnosis was calculated as weight in kilograms divided by the square of the height in meters.\textsuperscript{14} For patients older than 2 years, underweight was defined as BMI less than or equal to the 10th percentile, overweight as BMI greater than or equal to the 95th percentile, and middleweight as BMI greater than the 10th to less than the 95th percentile (11th-94th percentiles). For patients aged 1 to 2 years, greater than or equal to the 95th percentile and less than or equal to the 10th percentile of weight for
length were used to define overweight and underweight, respectively.14

The main outcome measures were remission status after courses 1 and 2 of chemotherapy, overall survival, and treatment-related mortality. Survival was defined as time from registration to death. Treatment-related mortality was defined as time until death from causes other than AML, censoring for progressive disease, relapse, and failure to enter remission after 2 courses of therapy. Patients lost to follow-up were censored at their last known date of contact. Patients in marrow remission (<5% marrow blasts) but without recovery of peripheral counts were censored at the end of course 2.

Toxicity grades 3 and 4 were defined by contemporary CCG toxicity grading criteria with protocol-specific modifications to capture details of anticipated gastrointestinal and hematopoietic toxicity.

This report analyzes data collected through January 9, 2004, with a median follow-up of 31 months and a range of 0 to 78 months. To compensate for the tendency for bad news (ie, deaths and relapses) to be reported sooner than ongoing follow-up for patients in continuing remission, events such as deaths and relapses were cen-

### Table 1. Demographics and Disease Characteristics According to Body Mass Index of Patients With De Novo AML*

|                        | Overweight (BMI ≥95%) (n = 114) | Middleweight (BMI 11%-94%) (n = 570) | Underweight (BMI ≤10%) (n = 84) | P Value
|------------------------|----------------------------------|-------------------------------------|---------------------------------|--------
| **Age, median (range), y** | 11.2 (1.3-19.0)                  | 11.0 (1.0-19.8)                     | 9.6 (1.1-19.7)                  | .44    .04
| **Male sex, No. (%)**    | 62 (54)                          | 299 (53)                            | 45 (54)                         | .78    .94
| **Race, No. (%)**        |                                 |                                     |                                 |        |
| White                   | 67 (60)                          | 378 (68)                            | 57 (69)                         | .18    .93
| Black                   | 16 (14)                          | 46 (8)                              | 7 (8)                           | .06    .88
| Hispanic                | 19 (17)                          | 100 (18)                            | 13 (16)                         | .96    .74
| Asian                   | 1 (1)                            | 20 (4)                              | 3 (4)                           | .23    >.99
| Other                   | 8 (7)                            | 16 (3)                              | 3 (4)                           | .04    .73
| Unknown                 | 3                                | 10                                  | 1                               |        |
| **White blood cell count, median (range), × 10⁹/L** | 27.9 (0.7-860)                  | 17.7 (0.5-684)                      | 13.9 (1.2-418)                  | <.001  .59
| **Morphology, No. (%)** |                                 |                                     |                                 |        |
| FAB M0                  | 8 (7)                            | 31 (6)                              | 3 (4)                           | .69    .61
| FAB M1                  | 22 (19)                          | 94 (17)                             | 17 (21)                         | .61    .50
| FAB M2                  | 37 (33)                          | 175 (31)                            | 19 (23)                         | .89    .16
| FAB M4                  | 25 (22)                          | 118 (21)                            | 26 (31)                         | .94    .05
| FAB M5                  | 16 (14)                          | 91 (16)                             | 14 (17)                         | .65    .99
| FAB M6                  | 0                                | 16 (3)                              | 2 (2)                           | .09    >.99
| FAB M7                  | 6 (5)                            | 27 (5)                              | 2 (2)                           | .97    .57
| Other                   | 0                                | 8 (1)                               | 0                               | .36    .61
| Unknown                 | 0                                | 10                                  | 1                               |        |
| **Marrow cytogenetics, No. (%)†** |                                 |                                     |                                 |        |
| Normal                  | 14 (22)                          | 91 (25)                             | 9 (18)                          | .74    .32
| Favorable               | 27 (43)                          | 127 (35)                            | 21 (41)                         | .30    .49
| Unfavorable             | 6 (10)                           | 8 (2)                               | 4 (8)                           | .01    .048
| Standard                | 16 (25)                          | 136 (38)                            | 17 (33)                         | .09    .67
| Unknown                 | 51                               | 208                                 | 33                              |        |
| **Treatment, No. (%)‡** |                                 |                                     |                                 |        |
| Phase 2                 |                                 |                                     |                                 |        |
| Regimen A               | 44 (46.8)                        | 245 (48.2)                          | 34 (50.7)                       | .89    .80
| Regimen B               | 45 (47.9)                        | 249 (49.0)                          | 30 (44.8)                       | .93    .60
| Phase 3                 |                                 |                                     |                                 |        |
| Related donor           | 10 (15.6)                        | 106 (28.1)                          | 20 (42.6)                       | .05    .06
| Received transplant     | 9 (14.1)                         | 91 (24.1)                           | 16 (34.0)                       | .11    .20
| Received cytarabine     | 53 (82.8)                        | 268 (71.1)                          | 26 (55.3)                       | .07    .04
| Phase 4                 |                                 |                                     |                                 |        |
| Interleukin 2           | 18 (54.5)                        | 88 (49.2)                           | 8 (47.1)                        | .71    .93
| Follow-up               | 15 (45.5)                        | 91 (50.8)                           | 9 (52.9)                        | .71    .93

Abbreviations: BMI, body mass index; FAB, French-American-British classification.9
*Numbers and percentages include only those with data.
†Cytogenetic results were available for 62% of patients.
‡Treatment is shown in Figure 1.
MORTALITY BY BMI IN CHILDREN WITH ACUTE MYELOID LEUKEMIA

Table 2. Response to Therapy and Events and Outcomes According to BMI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Overweight (BMI &gt;95%) (n = 114)</td>
<td>Middleweight (BMI 11%-94%) (n = 570)</td>
</tr>
<tr>
<td>Blasts in marrow on day 14, %</td>
<td>&lt;5 77 (81)</td>
<td>400 (84)</td>
</tr>
<tr>
<td></td>
<td>≥5 18 (19)</td>
<td>79 (16)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>19</td>
<td>91</td>
</tr>
<tr>
<td>At end of course 1</td>
<td>Remission 94 (85)</td>
<td>508 (91)</td>
</tr>
<tr>
<td></td>
<td>Treatment failure 9 (8)</td>
<td>28 (5)</td>
</tr>
<tr>
<td></td>
<td>Death 8 (7)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>At end of course 2</td>
<td>Remission 64 (82)</td>
<td>377 (89)</td>
</tr>
<tr>
<td></td>
<td>Treatment failure 1 (1)</td>
<td>25 (6)</td>
</tr>
<tr>
<td></td>
<td>Death 13 (17)</td>
<td>23 (5)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.
*Not all patients had day 14 marrow results reported.

RESULTS

Of 768 patients at diagnosis, 114 (14.8%) were overweight and 84 (10.9%) underweight. Table 1 lists demographic features of overweight, middleweight, and underweight patients, characteristics of their AML, and their treatment assignments. The 3 BMI groups did not differ significantly in distribution by sex, ethnicity or race, or the proportion of patients with incomplete data. Compared with middleweight patients, overweight patients had higher leukocyte counts (P = .001), were marginally more likely to have unfavorable marrow cytogenetics (P = .01), were less likely to have a related marrow donor for marrow transplantation (P = .05), but were equally likely to actually undergo transplantation (9/10 vs 91/106). Underweight patients were younger (P = .04) and more commonly had unfavorable marrow cytogenetics (P = .048).

Table 2 shows the response to therapy for the 3 BMI groups. In course 1, there were no differences in the early response rate as measured by the day 14 marrow blast percentage or in treatment failure rate. There was a trend for a reduced remission rate and an increased death rate among overweight patients, whereas the underweight patients showed a definite reduction in remission rate and increase in death rate. At the end of course 2, compared with middleweight patients, overweight patients were significantly more likely to die (17% vs 5%, P = .001). The actuarial survival after study enrollment of underweight and overweight patients was inferior to that of middleweight patients (FIGURE 2).

After course 1, the univariate HR for treatment-related mortality was significantly increased in the overweight patients (HR, 2.12; 95% CI, 1.37-3.28; P = .001) and the underweight patients (HR, 1.80; 95% CI, 1.06-3.06; P = .03) compared with the middleweight patients (TABLE 3). Survival from study entry was reduced in the overweight patients (HR, 1.47; 95% CI, 1.09-1.98; P = .01) and the underweight patients (HR, 1.42; 95% CI, 1.00-2.03; P = .05). From the end of course 2, there were no differences in survival among the 3 groups or in relapse rates or treatment-related mortality.

Table 3 shows the multivariate analysis of HR for survival and treatment-related mortality adjusted for age, race, WBC count, cytogenetics, and allogeneic bone marrow transplantation for the patients with complete data for the 5 variables. After adjustment, overweight and underweight groups were still less likely to survive than middleweight patients, and HR for treatment-related mortality was even higher than in univariate analysis.
TABLE 4 lists deaths according to when they occurred and attribution of cause. Compared with middleweight patients, overweight and underweight patients were more likely to die before or during their first remission (P = .002 and P = .047, respectively). In all groups, infection was the most common cause of death before or during remission. After recurrence of AML, the most common cause of death was AML itself in all 3 groups.

Excessive treatment-related mortality suggests that overweight and underweight patients could be receiving too much chemotherapy. To address this issue, first we examined the doses of protocol therapy actually received. Then we compared toxicity grades 3 and 4, time to neutrophil recovery, and duration of course as indirect measures of drug effect on normal marrow. Of 768 patients, 10 received less than or equal to 90% of dosing of course 1 therapy according to square meters: in 6 (1 underweight, 1 overweight, and 4 middleweight) of these 10 patients, doses were reduced according to protocol guidelines for hyperbilirubinemia. Four overweight patients received reduced doses calculated to fall between their actual weight and their ideal body weight. Overweight patients were significantly more likely to have a dose reduction than middleweight patients: 4.8% vs 0.7% (P = .006).

Toxicity grades 3 and 4 were assessed from a menu of 45 clinical and laboratory parameters. Compared with middleweight patients, more overweight patients experienced grade 3 or 4 abdominal pain (P = .05), systolic hypertension (P = .02), pulmonary function abnormalities (P = .03), and coagulopathy (P < .001), whereas more underweight patients experienced grade 3 or 4 elevations of hepatic enzymes (alanine aminotransferase, P = .01; and aspartate aminotransferase, P = .04).

Death from infection increases in direct proportion to the magnitude and duration of neutropenia.15 Hematologic toxicity was probably the most rel...
evant complication for this study. Important landmarks for assessing neutropenia are time to an ANC of 500 × 10^9/L (the time when empirical antibiotics are typically discontinued) and time to an ANC of 1000 × 10^9/L (the time when the patient may be able to begin the next chemotherapy course). Within 5 weeks of the start of therapy, 79.5% of middleweight patients who continued to course 2 had an ANC of greater than or equal to 500 × 10^9/L, which was not different from the 87.2% of overweight patients (P = .11) or 77.6% (P = .84) of underweight patients. At 7 weeks, the respective proportions were 97.2%, 98.9%, and 100%. The time to recovery of ANC of 1000 × 10^9/L after the start of course 1 for the 3 groups was plotted (FIGURE 3): overweight and middleweight patients had significantly faster neutrophil recovery than underweight patients (P = .004).

The time to complete a course of therapy was another indicator of toxicity. Figure 3 shows duration of course 1 in the 3 groups: there was no significant difference in the duration of the course. When patients who had dose reductions were excluded, the relative

<table>
<thead>
<tr>
<th>Table 4. Causes of Death</th>
<th>No. (%)</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Overweight (BMI ≥95%) (n = 114)</td>
<td>Middleweight (BMI 11%-94%) (n = 570)</td>
</tr>
<tr>
<td>Deaths before or during remission</td>
<td>30 (26)</td>
<td>78 (14)</td>
</tr>
<tr>
<td>AML related</td>
<td>1 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Treatment related</td>
<td>29 (25)</td>
<td>73 (13)</td>
</tr>
<tr>
<td>Infection</td>
<td>20 (18)</td>
<td>44 (8)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td>0 (0)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Relapse</td>
<td>38 (33)</td>
<td>205 (36)</td>
</tr>
<tr>
<td>Deaths after relapse</td>
<td>28 (25)</td>
<td>135 (24)</td>
</tr>
<tr>
<td>AML related</td>
<td>16 (14)</td>
<td>72 (13)</td>
</tr>
<tr>
<td>Treatment related</td>
<td>12 (11)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Infection</td>
<td>9 (8)</td>
<td>37 (6)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2 (2)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Toxicity</td>
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</tr>
<tr>
<td>Graft-vs-host disease</td>
<td>1 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>8 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; BMI, body mass index.

Figure 3. Kaplan-Meier Plots of the Cumulative Incidence of Recovery to an Absolute Neutrophil Count of at Least 100 000 × 10^9/L According to BMI and Cumulative Incidence of Entry to Course 2

BMI indicates body mass index.

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positions of the 3 groups were unchanged.

COMMENT

This study shows that overweight and underweight children and adolescents with AML are less likely to survive than patients with BMI in the 11th through 94th percentiles. Inferior survival in both extreme BMI groups is attributable to early treatment-related mortality, and treatment-related mortality is mostly from infection. Although there is already substantial evidence that underweight children with acute lymphoblastic leukemia and solid tumors experience increased relapses and reduced survival,16-19 this is the first study to our knowledge to show excess mortality in overweight pediatric cancer patients. These results contrast with those in most adult cancers in which underweight patients have no excess mortality and overweight patients have excess cancer-related death rather than death from excessive toxicity.20-25 One notable exception is marrow transplantation: 3 studies show excess mortality in obese adults from a combination of relapse and treatment-related mortality26,27 or treatment-related mortality alone.28 Dickson et al28 also found that underweight patients experienced higher treatment-related mortality. Marrow transplantation and contemporary AML therapy have in common dose-intensive chemotherapy complicated by a relatively high baseline treatment-related mortality that is exaggerated among underweight and overweight patients.

Malnutrition is associated with advanced disease, lower socioeconomic status, immunodeficiency, increased number and spectrum of infections, reduced access to care, and delays in diagnosis.18,19,20 Even after adjustment for socioeconomic status, malnutrition continues to be associated with poor outcome. Malnutrition in children reduces absorption, decreases drug-protein binding, and impedes oxidative and other metabolic reactions. These effects increase half-life, reduce clearance, and impair glomerular filtration of drugs.30 They also augment toxicity.30 There is no information about the pharmacology of cancer chemotherapy in underweight patients. Busulfan is the only drug for which there is dosing information according to weight or BMI distribution in children.31 Malnutrition reduces survival in children with cancer in direct proportion to the extent of their malnutrition.18,19,20 Correction of nutritional status improves outcomes.28 Thus, it would seem reasonable to determine whether delaying therapy to initiate nutritional supplementation and correction of immunodeficiency is possible, and if correction is possible, to determine whether it improves outcome.

There is no obvious solution to the problem of excess treatment-related mortality in overweight patients. The data concerning neutrophil recovery and duration of course do not support the hypothesis that overweight patients in this study received too much chemotherapy. There are few traditional pharmacologic studies of bioavailability of chemotherapeutic agents in obese adults and none in overweight children or adolescents. Several small studies have investigated bioavailability of cyclophosphamide, ifosfamide, doxorubicin, and its metabolite doxorubicinol as single agents.32-34 Combination chemotherapy has been investigated in 1 obese patient: compared with normal-weight patients, she showed a substantially increased concentration over time for 4-hydroxy cyclophosphamide, thiotepa, and carboplatinum.35 Because in general these pharmacologic studies show a trend for reduced clearance and longer half-lives of chemotherapeutic agents, they seem to contradict studies of antibiotics in obese adults in which hyperfiltration increases clearance.36 Because most recent studies show reduced rather than excessive toxicity among obese individuals, today the consensus is that obese adult cancer patients receive too little rather than too much chemotherapy.21-25

In this study, overweight patients experienced more severe abdominal pain, hypertension, pulmonary dysfunction, and coagulopathy. Unfortunately, the information collected does not indicate when these toxicities occurred, how long they lasted, or whether they contributed to death or reflected end-stage deterioration. Comorbidities such as these increase risk of death in adult cancer patients with febrile neutropenia, so they may be important in these patients.37 Overweight patients can also manifest subtle immunologic abnormalities that could contribute to excess infectious death.38,39 In 1970, Wiernik and Serpick40 described 8 morbidly obese patients among 106 adults with AML. None of the 8 patients survived longer than 1.75 months compared with a median survival of 3.5 months for the whole study. These authors postulate that subclinical diabetes, difficulties in performing thorough physical examinations, or nuances in carrying out routine nursing care could contribute to early demise.40

This study has the limitations of a retrospective study: CCG-2961 was not designed to investigate BMI as a variable. Some findings, such as the proportion of overweight and underweight patients with donors for marrow transplantation, may be spurious. The study does not illuminate the causes of excess infectious treatment-related mortality. There are no socioeconomic data. All assessments pertain to weight at diagnosis; it was not possible to determine whether weight gain in underweight patients or weight loss in overweight patients improved outcomes after the first course. Finally, it is likely that the observation of excessive treatment-related mortality in overweight patients will be reproducible only in pediatric cancers that involve extremely dose-intensive chemotherapy or marrow transplantation studies as in obese adults.

The effect of BMI on outcome in pediatric AML is not a trivial problem: the reduced survival in underweight and overweight patients is roughly equal to the improved survival accomplished by 10 years of progress in pediatric AML. Treatment-related mortality is the worst possible outcome for an individual enrolled in a clinical trial, and if treatment-
related mortality is not countered by a net gain in survival, excess treatment-related mortality is also the worst possible outcome for a clinical trial. These results have implications for clinicians and clinical investigators. This is the first example of immediate rather than impending life-shortening effects of excess weight in the young and a confirmation of the risks of undernutrition in other pediatric cancers.6-10 Interventions currently available that could reduce the treatment-related mortality in underweight and overweight groups include formal nutritional and immunologic assessment at diagnosis. Underweight patients could benefit from preemptive nutritional intervention or intravenous γ-globulin. In overweight patients, correction of persistent moderate hyperglycemia and hypertension may remediate 2 important comorbidities. Maintaining blood glucose concentration between 80 and 120 mg/dL appears to reduce mortality in patients in intensive care units.11 However, systematic changes in management should take place as part of controlled studies. Basic pharmacokinetic and pharmacodynamic studies of chemotherapeutic drug disposition in underweight and overweight patients are likely to provide a rational basis for dosing. Until such information is available, it is impossible to know whether doses of chemotherapy should be reduced. Dose reduction is likely to lead to increased relapse, but relapse is the lesser of 2 evils. It is also possible that dose reduction increases relapse and has no effect on toxic mortality. Finally, technologists, nurses, and physicians should examine whether overweight patients are receiving suboptimal care because of difficulties in assessing them, as suggested by Wiernik and Serpick.10 If that is the case, then it must be determined as to how to change practice to overcome these barriers.

Author Contributions: Drs Lange and Alonzo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lange, Feusner, Skolnik, Sacks, Smith, Alonzo.

Acquisition of data: Lange, Feusner, Sacks, Smith, Alonzo.

Analysis and interpretation of data: Lange, Gerbing, Feusner, Skolnik, Sacks, Smith, Alonzo.

Drafting of the manuscript: Lange, Gerbing, Skolnik, Sacks, Smith, Alonzo.

Critical revision of the manuscript for important intellectual content: Lange, Feusner, Skolnik, Sacks, Smith, Alonzo.

Study supervision: Lange, Feusner, Smith.

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REFERENCES

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If we knew what we were doing, it wouldn't be called research, would it?
—Albert Einstein (1879-1955)