Prediction of CR following a second course of '7+3' in patients with newly diagnosed acute myeloid leukemia not in CR after a first course

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'7+3' (7 days of cytarabine overlapping with 3 of daunorubicin or idarubicin) is probably the most commonly used remission induction regimen in adults aged ⩽60 with untreated AML. Cooperative group protocols typically call for a second 7+3 if the first is unsuccessful. Here we suggest that this recommendation often goes unheeded and discuss the consequences for patient care and interpretation of clinical trials.

In all, 1505 people, median age 53 years, received 7+3 on one of four SWOG protocols.[1–4] Together with cytarabine, three protocols[1–3] (enrolling 910 subjects) called for daunorubicin 45 mg/m^2 daily × 3 days, whereas in the fourth protocol (S0106),[4] 595 subjects were randomly assigned to cytarabine and either daunorubicin 60 mg/m^2 daily × 3 or daunorubicin 45 mg/m^2 daily × 3+gemtuzumab ozogamicin 6 mg/m^2 on day 4. Out of 1505 people, 140 (9%, range 3–18% on the 4 protocols) died within 28 days of initiation of treatment and 727 (48%, 41–60%) attained complete remission (CR) on the first course. Thus, 638 people were alive but not in CR after course 1; 81% had >5% blasts in 'day 14' or subsequent marrow, whereas 19% had failure of count recovery.

Although the protocols called for a second 7+3 in people judged refractory to the first, only 333 of the 638 patients (52%, range 40–57%) did so. Lest it appear that this is a peculiarity of SWOG, Dr Tallman informed us (personal communication) that ~ 50% of Eastern Cooperative Oncology Group patients on protocol E1900 also did not receive a second 7+3 after failure of the first despite protocol stipulations that they do so. These data suggest that there is considerable uncertainty about management of subjects not in CR after a first 7+3. Data from only the SWOG protocol for which relevant data are available (S0106) indicate that 76% of the 97 people who did not receive a second 7+3 (out of 216 S0106 patients not in CR after course 1) received alternative chemotherapy, 6% received a transplant and 7% no further therapy, with 10% lost to follow-up. Neither pre-treatment covariates (for example, age, cytogenetics and performance status) nor post-treatment covariates (for example, day 14 marrow findings alone or compared with pre-treatment) were associated with receipt of a second course. Only treatment at a 'non-academic center' was so associated, with such patients 7.29 times more likely to receive a second 7+3, perhaps reflecting the fewer alternative regimens available in non-academic settings. However, as quantified by the area under receiver-operating characteristic curves (value 1.0 = perfect prediction, 0.5 = a coin flip), the ability of a multivariable model (Table 1) to predict which people received a second 7+3 was only fair (area under the receiver operating characteristic curve (AUC) = 0.68). Hence, other than the possible biases inherent in the type of patient treated at an academic center, we could not identify any systematic biases prompting receipt of a second 7+3 rather than alternative therapies.

Presumably, the decision to not give a second 7+3 reflects a belief that alternative approaches are superior. Our data suggest problems with this belief. The CR rate on a second 7+3 was 43% with an early death rate of 10% (versus 48% and 9% on a first 7+3). Furthermore, none of the covariates noted above, including day 14 marrow blasts or cellularity, or change in these versus pre-treatment, or the day a second 7+3 began, was associated with or predicted second course CR (AUC = 0.68 for the multivariable model shown in Table 2). Conclusions were the same regardless of protocol, or whether we restricted attention to people receiving daunorubicin at 60 mg/m^2 daily × 3, or who had >5% blasts when course 2 began or began course 2 within 35 days of course 1, or when day 14 WBC and peripheral blood blasts percent were included (available for S0106). Although National Cancer Research Institute/ Medical Research Council data[5,6] suggest that people with >15% marrow blasts on day 14 are much less likely to enter CR on a second course, using such a 15% cutoff did not materially affect ability to predict CR on a second 7+3 (multivariable AUC = 0.70 with 15% cutoff versus 0.68 using actual day 14 blast %), perhaps reflecting various differences between National Cancer Research Institute/ Medical Research Council therapies and 7+3. Kern *et al.*[7] noted that higher day 16 blasts % was associated with lower CR rate; their subjects received a high-dose cytarabine-containing regimen (S-HAM) rather than a second 7+3, and the median day 16 marrow blast percent was 5% in contrast to 20% on day 14 in our subjects. Although our subjects who entered CR after receipt of two courses of 7+3 had inferior survival and relapse-free survival than patients who did so after one course on univariate analysis, multivariable analysis showed this reflected pre-treatment age, and cytogenetics, rather than courses to CR.

An important question is how outcomes following a second 7+3 compare with those following alternative approaches. The only data available to us indicate that survival in S0106 was similar regardless of whether patients received a second 7+3 or alternative therapies, for example, those containing 'high-dose' cytarabine as might be given in a clinical trial at an 'academic' center. We acknowledge that we have incomplete information regarding important covariates and the relatively crude nature of survival as an outcome. Even with more

Table 1. Multivariable logistic regression model for receiving a second course of 7+3 versus treatment off-protocol (alternative chemotherapy or transplant) after failing the first course in S0106 (119 people received a second 7+3 and 96 did not)

	OR	*95% CI*	P-*value*
Non-academic (ref = academic)	7.29	(1.61, 33.02)	0.0099
Age (years)	0.98	(0.94, 1.03)	0.49
PS 2-3 (ref = PS 0-1)	1.31	(0.22, 7.99)	0.77
Unfavorable cyto (ref = not unfavorable cyto)	1.34	(0.45, 3.98)	0.6
Day 14 marrow blasts (%)	1.01	(0.97, 1.04)	0.76
Day 14 cellularity (%)	0.99	(0.96, 1.01)	0.41
Day 14 infiltrate	1.00	(0.94, 1.06)	1
Day 14 blood blasts (%)	0.99	(0.96, 1.02)	0.67
Day 14 WBC (×10^3)	0.89	(0.77, 1.02)	0.085

Abbreviations: CI, confidence interval; OR, odds ratio; PS, performance status; WBC, white blood cell count.

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Table 2. Multivariable logistic regression for CR with a second course

	OR	*95% CI*	P-*value*
Age (years)	0.98	(0.95, 1.02)	0.27
PS 2-3 (ref = PS 0-1)	0.5	(0.17, 1.48)	0.21
Unfavorable cytogenetics (ref = other cytogenetics)	0.62	(0.28, 1.4)	0.25
Day marrow	1	(0.93, 1.09)	0.95
Day second course	0.99	(0.94, 1.04)	0.68
Marrow blasts (%)	0.99	(0.94, 1.03)	0.56
Change in blasts	1.01	(0.97, 1.05)	0.67
Cellularity	0.99	(0.95, 1.03)	0.58
Change in cellularity	1.01	(0.97, 1.05)	0.53
Infiltrate	1.01	(0.94, 1.09)	0.74
Change in infiltrate	0.99	(0.94, 1.04)	0.64
Secondary AML (ref = *de novo* AML)	0.48	(0.08, 2.93)	0.43
S8600 7+3 (ref = S0106 7+3)	0.63	(0.07, 6.09)	0.69
S9031 7+3 (ref = S0106 7+3)	0.4	(0.08, 1.94)	0.26
S9333 7+3 (ref = S0106 7+3)	0.95	(0.2, 4.59)	0.95
S0106 GO (ref = S0106 7+3)	0.71	(0.25, 1.99)	0.52

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; GO, gemtuzumab ozogamicin; OR, odds ratio; PS, performance status. 333 people, 143 CR.

information, the value of a second 7+3 versus other approaches can only be addressed in a randomized trial. Although such a trial has yet to be undertaken, our data suggest that the chance of benefit from a second 7+3 is sufficiently high to make such a trial reasonable and, by extension, also to make administration of a second 7+3 an acceptable option outside the context of a trial. In particular, although CR rates and early death rates following a second 7+3 were similar to those following a first, we could not identify people more/less likely to benefit from a second 7+3, and achievement of CR only after a second 7+3 was not independently associated with shorter survival or RFS.

Although we strongly advocate randomization between a second 7+3 and alternative therapies, this may never be done. Many people not in CR after a first 7+3 will probably continue to receive new therapies in single-arm phase 2 clinical trials. Such trials typically target a minimum (null) CR rate of 20–25%, that is, accrual on the trial stops only once it is clear the response rate is not better than 20–25%. Our results indicate problems with this approach. If CR rates on a second course of 7+3 are 40–45%, null CR rates of 20–25% in trials including people not in CR after one course of 7+3 can lead to false-positive results for regimens, with true CR rates very similar to or even worse than what could be obtained with a second course of 7+3. In practical terms, people could continue receiving the new therapy even after it becomes likely that it is not as effective as a second 7+3. Pending information from a trial randomizing between a second 7+3 and alternative therapy, we believe minimum (null) CR rates should be set at 40–45% in phase 2 trials including people whose AML does not respond to a first course of 7+3. As a corollary, the criterion for AML refractory to 7+3 should be a failure to attain CR after two, not one, courses of 7+3.

Further, the observation that approximately half of the people failing a first course of 7+3 were removed from study and therefore defined as 'treatment failures', even though we could find no evidence they would be more or less likely to benefit from a second cycle of 7+3 than the remainder of people, should be kept in mind when comparing trials of different induction intensities. Let us assume a more intense therapy produces 60 CRs among 100 people receiving a first course and 8 CRs among the 40 people not in CR after course 1 but who receive course 2; similar first and second course CR rates (60% and 20%, respectively) have been reported following the use of high-dose cytarabine-containing induction regimens.[8] Thus, the overall CR rate is 68/100. If a similar group of 100 subjects receives a first course of 7+3 with 49 entering CR, and if all 51 not entering CR receive a second 7+3, with 22 entering CR (corresponding to the CR rates of 49% and 43% on a first and second 7+3 seen here, respectively), the overall CR rate is approximately the same (71/100). However, to the extent to which people failing a first 7+3 do not receive a second (the second course CR rate being higher with 7+3 compared with higher-dose regimens[8]), the overall CR rate with 7+3 will appear lower; if only 50% of the 51 patients in the above scenario not in CR after the first 7+3 receive a second, the overall CR rate will only be 49% $+(26 \times 43\%) = 60\%$. Unless physicians participating in trials comparing therapies of different intensities consistently treat patients with the stipulated second cycle of induction, the conclusions of these trials could be, at best, muddled and very possibly incorrect.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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