CORRESPONDENCE

Oral Azacitidine Maintenance for Acute Myeloid Leukemia

TO THE EDITOR: In their article describing the use of an oral formulation of azacitidine (CC-486) as maintenance therapy in older patients with acute myeloid leukemia (AML), Wei et al. (Dec. 24 issue)[1] report that patients who were treated with CC-486 had significantly longer overall and relapse-free survival than those who received placebo. Given the median age (68 years) and good performance status of the patients in this trial, the low number of patients who completed adequate consolidation treatment before randomization is worrisome because of the proven benefits of postremission therapy in AML.[2-5] As such, the characterization of postprotocol therapy is essential for understanding outcomes. The authors state that the median duration of relapse-free survival "probably explains" the longer duration of overall survival with CC-486. However, the use of "low-intensity" salvage therapy (e.g., placebo, hydroxyurea, and low-dose cytarabine) could also have contributed to this finding. Thus, it would be helpful for the authors to specify which reinduction regimens were used and the frequency of administration, since not all low-intensity therapies are created equal. Given these concerns, it is unclear whether CC-486 should become the standard of care, especially when adequate postremission consolidation therapy and reinduction therapy are provided.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Intensive postremission consolidation therapy is standard for younger patients with AML. Among older patients, the benefit of such therapy is unclear, and the most effective dosing intensity and number of consolidation cycles have not been established (Table 1).[1-5] Several studies have suggested that the percentage of patients who receive no consolidation therapy ranges from 10 to 22%. In our trial, 80% of the patients received at least one intensive consolidation cycle and 35% received two or more cycles. Overall survival was longer in the CC-486 group than in the placebo group, regardless of whether patients had received no consolidation cycles (23.3 months vs. 10.9 months), one cycle (21.0 months vs. 14.3 months), or two or more cycles (28.6 months vs. 17.6 months). More patients received postprotocol therapy in the placebo group than in the CC-486 group (73% vs. 58%), including more frequent use of postprotocol intensive chemotherapy (38% vs. 29%) or allogeneic stem-cell transplantation (14% vs. 6%) (Table S10 in the Supplementary Appendix of the article, available with the full text of the article at NEJM.org). Therefore, there is no evidence that the trial outcomes were influenced by an imbalance with respect to salvage-therapy options provided to patients in the CC-486 group.

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Since publication of their article, Dr. Wei reports serving on the advisory boards for Roche, Pfizer, Agios, and Gilead; Dr. Döhner, receiving consulting fees from GEMoaB, Gilead, Berlin-

Table 1. Randomized Postremission Trials Involving Older Patients with AML.*

Reference	Age of Patients	Consolidation Therapy	Median Duration of Overall Survival	Consolidation Cycles Completed
	yr			*no. of cycles (% of patients)*
Mayer et al.[1]	>60	SD cytarabine for 4 cycles†	NA	4 (71)
		ID cytarabine for 4 cycles‡	NA	4 (66)
		HD cytarabine for 4 cycles§	NA	4 (29)
Stone et al.[2]		No consolidation therapy	NA	0 (18)
	≥60	SD cytarabine for 4 cycles†	19.2 mo	4 (71)
		ID cytarabine plus mitoxantrone for 2 cycles¶	15.6 mo (NS)	2 (78)
Goldstone et al.[3]	≥60	DAT‖	Approximately 15 mo	1 (98)
		DAT, COAP, DAT, COAP in sequence**	Approximately 15 mo (NS)	1 (16), 2 (26), 3 (12), and 4 (61)
Büchner et al.[4]	>60	TAD maintenance for 3 yr††	19 mo	0 (10), TAD (20), and maintenance (70)
		TAD†† and S-HAM‡‡	21 mo (NS)	0 (11), 1 (38), and 2 (51)
Gardin et al.[5]	≥65	Intensive 7+4 for 1 cycle§§	37% at 24 mo	0 (22)
		Ambulatory 5+1 for 6 cycles¶¶	56% at 24 mo (P=0.03)	1 (93) and 6 (82)

* AML denotes acute myeloid leukemia, NA not available, and NS no significant between-group difference.
† Treatment consists of standard-dose (SD) cytarabine (100 mg per square meter of body-surface area) once daily for 5 days.
‡ Treatment consists of intermediate-dose (ID) cytarabine (400 mg per square meter) once daily for 5 days.
§ Treatment consists of high-dose (HD) cytarabine (3000 mg per square meter) twice daily on days 1, 3, and 5.
¶ Treatment consists of intermediate-dose (ID) cytarabine (500 mg per square meter) twice daily plus mitoxantrone (5 mg per square meter) twice daily for 6 doses.
‖ DAT consists of daunorubicin (50 mg per square meter on days 1, 3, and 5), cytarabine (100 mg per square meter twice daily on days 1 through 10), and thioguanine (100 mg per square meter twice daily on days 1 through 10).
** COAP consists of cyclophosphamide (600 mg per square meter on day 1), vincristine (1.5 mg per square meter on day 1), cytarabine (100 mg per square meter on days 1 through 5), and prednisolone (60 mg per square meter on days 1 through 5).
†† TAD consists of cytarabine (100 mg per square meter on days 1 and 2, then twice daily on days 3 through 8), daunorubicin (60 mg per square meter on days 3 through 5), thioguanine (100 mg per square meter twice daily on days 3 through 9), then maintenance with subcutaneous cytarabine (100 mg per square meter twice daily for 5 days), daunorubicin (45 mg per square meter on days 3 and 4 [course 1]), thioguanine (100 mg per square meter twice daily on days 1 through 5 [course 2]), and cyclophosphamide (1 g per square meter on day 3 [course 3]), thioguanine (course 4), and restarting with course 1.
‡‡ S-HAM consists of cytarabine (500 mg per square meter twice daily on days 1, 2, 8, and 9) plus mitoxantrone (10 mg per square meter on days 3, 4, 10, and 11).
§§ Treatment (known as 7+4) consists of cytarabine (200 mg per square meter once daily for 7 days) plus daunorubicin (45 mg per square meter) or idarubicin (9 mg per square meter) once daily for 4 days.
¶¶ Treatment (known as 5+1) consists of subcutaneous cytarabine (60 mg per square meter twice daily) for 5 days with daunorubicin (45 mg per square meter) or idarubicin (9 mg per square meter) on day 1.

Chemie, and Pfizer; and Dr. Roboz, receiving consulting fees from Amgen, Bristol Myers Squibb, GlaxoSmithKline, MEI Pharma, Mesoblast, and Roche/Genentech. No further potential conflict of interest relevant to this letter was reported.

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