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CORRESPONDENCE

WILEY AJH

Impact of fludarabine-based induction therapy on outcome of FLT3−/NPM1+ cytogenetically normal acute myeloid leukemia

To the Editor:

We have read with great interest the manuscript by Sayar et al. entitled "Long-term outcome of NPM1 mutated acute myeloid leukemia: A single-institution experience."[1] The Authors report on 12 patients with cytogenetically normal acute myeloid leukemia (CN-AML) with mutated nucleophosmin (NPM1+) and unmutated FLT3 (FLT3−). Despite a high complete remission (CR) rate with standard (7 + 3 cytarabine and idarubicin) induction chemotherapy, all patients relapsed within 41 months, with a median relapse-free survival (RFS) of 16.5 months. Eight out of 11 patients achieved a second CR, 6/8 underwent allogeneic stem cell transplantation, and 3/6 patients are alive 6-18 months after transplant.

We reviewed our database and identified 51 patients treated for FLT3−/NPM1+ CN-AML. There were 26 males and 25 females, with a median age of 60 years (20-77). Induction chemotherapy consisted of fludarabine, cytarabine, and idarubicin in 34 patients and non-fludarabine-based (3 + 7 or hypomethylating agents—HMA) in 17 patients. All patients achieving CR received consolidation chemotherapy with 1-2 courses of high-dose cytarabine and idarubicin. Patients considered at high risk of relapse for disease characteristics at diagnosis (hyperleukocytosis, secondary AML) or poor response to induction therapy were considered candidates for allogeneic stem cell transplantation (SCT) from sibling or unrelated donors.

Overall, 41/51 patients (80%) achieved CR after induction therapy; CR rate was significantly higher in patients receiving fludarabine-based induction (31/34, 91%) compared to the non-fludarabine group (10/17, 59%; $\chi^2 = 12.4$; $P < .001$). Of the 40 patients attaining CR who were evaluable (1 was lost to follow-up), 27 maintained remission while 13 (32.5%) relapsed, with a 3-year RFS of 67%, without difference in patients receiving or not fludarabine in induction (69% vs. 58%). Twelve patients underwent allogeneic SCT in first line for high-risk features or poor response to induction therapy, while five patients were transplanted after relapse and reinduction. Overall survival (OS) at 3 years was 53%, with a significant correlation according to induction therapy: 3-year OS for patients receiving fludarabine was 64% compared to 32% in patients treated with 3 + 7 or HMA ($P = .0012$) (Figure 1).

*Conflict of interest: nothing to report.

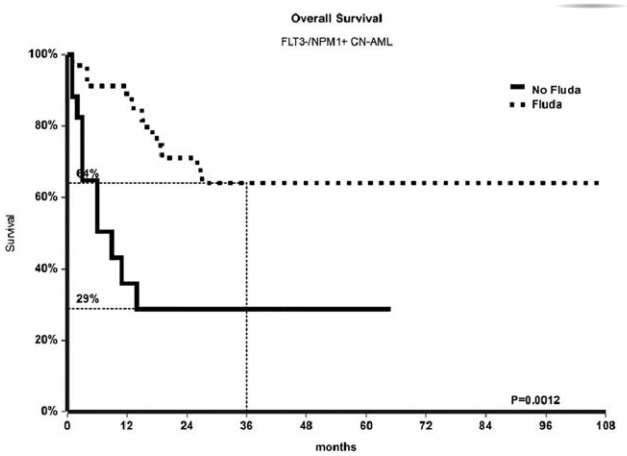

FIGURE 1 Overall Survival according to induction therapy

Based on our previous observation of a negative impact of ABCG2 over-expression in AML,[2] we analyzed the impact of ABCG2 expression in this cohort of FLT3-/NPM1+ CN-AML patients. ABCG2 was over-expressed in 29/51(57%) cases. As previously reported, ABCG2 status did not impact on CR rates (23/29, 79% in ABCG2+ and 18/22, 82% in ABCG2− patients), independently of the induction type. There was a trend for a lower 3-year RFS (61% vs. 74%) and 3-year OS (43% and 68%) in ABCG2 overexpressing patients, that however did not reach statistical significance ($P = .2$ for RFS and $P = .09$ for OS), probably due to the limited number of cases. Combining induction therapy and ABCG2 status, we found the best outcomes in ABCG2− patients receiving fludarabine (3-year DFS and OS 84%), while the few non-fludarabine treated ABCG2− patients had a dismal prognosis (3-year DFS and OS 20% and 33%, respectively). As expected,[3] in ABCG2+ cases, fludarabine was not able to completely overcome the negative impact of ABCG2 expression, as long-term survival of fludarabine-treated patients was non-statistically superior compared to those receiving 3 + 7 or HMA (3-year OS 50% vs. 33%, $P = .08$).

Although it is generally recognized that FLT3−/NPM1+ CN-AML patients have a favorable survival probability, comparable to that of core-binding factor leukemia,[4] some experiences have reported a rather unsatisfactory long-term outcome, with 2- or 3-years RFS around 30%.[1,5] Our experience confirms the high CR rate, particularly using fludarabine-based induction chemotherapy, but also quite long relapse-free and overall survivals (67% and 53% at 3 years, respectively). We and others[6] have found that inclusion of fludarabine in induction course was associated with excellent CR rates, relatively high OS, and acceptable toxicity. Over-expression of multidrug resistance proteins, such as ABCG2, could contribute to a higher relapse risk and inferior survival, though reasons of AML recurrence still need to be fully explained.

In conclusion, our data support the use of a more intensive approach also in patients with FLT3−negative, NPM1-mutated

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CN-AML. However, further efforts are needed to identify risk factors for AML recurrence in this "favorable-risk" patients and, ultimately, to optimize their management.

Mario Tiribelli, Antonella Geromin, Daniela Damiani
Division of Hematology and BMT, Department of Experimental and Clinical Medical Sciences, Azienda Sanitaria Universitaria Integrata, Udine, Italy

Correspondence
Daniela Damiani, MD, Division of Hematology and BMT, Azienda Sanitaria Universitaria Integrata di Udine, P.le S. M. Misericordia, 15-33100 Udine, Italy.
Email: daniela.damiani@uniud.it

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