

“Dexamethasing” acute myeloid leukemia: new opportunities for an “old” drug

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Dexamethasone is a central component in the treatment of lymphoid neoplasias, but its use in the treatment of myeloid neoplasias has not yet been well established. However, it may be considered an emerging field, as data are being generated from different aspects of acute myeloid leukemia (AML) treatment. In addition, recently published mechanistic studies are underscoring its possible role as agent with antileukemic activity in AML. Previous studies showed that AML with hyperleukocytosis at initial diagnosis is associated with an increased risk of early death.^{1,2} Patients with AML and hyperleukocytosis frequently suffer from leukostasis or organ infiltration (of the lungs, CNS, kidneys, myocardium, etc.)³ as well as disseminated intravascular coagulopathy and tumor lysis syndrome, contributing to morbidity and mortality.⁴ Hyperleukocytosis in AML is also an independent risk factor for relapse after successful induction chemotherapy² and is associated with AML-specific mutations affecting cell signaling and DNA methylation, such as *FLT3-ITD*, *NPM1*, *DNMT3A*, *TET2* and *NRAS*⁵ and monocytic (FAB M4/M5) blast morphology.¹

In two large retrospective studies, the addition of dexamethasone to induction chemotherapy improved overall survival in patients with AML, and hyperleukocytosis and was associated with lower early death and reduced relapse incidence.^{6,7} Prior to these landmark studies, it had already been very well established that dexamethasone plays a central role in the prophylaxis and therapy of all-trans retinoic acid-/arsenic trioxide-induced differentiation syndrome, improving outcome of patients with acute promyelocytic leukemia, and dexamethasone is also recommended for treatment of differentiation syndrome induced by other epigenetically active agents, such as IDH inhibitors.⁸ Mechanistically, *in vitro* studies demonstrated enhanced dexamethasone sensitivity in cytarabine-resistant AML cells,⁹ suggesting that dexamethasone might improve out-

come of patients with AML beyond those with hyperleukocytosis. More recently, Ahmed *et al.*¹⁰ provided an interesting model for the antileukemic activity of dexamethasone in non-M3 AML. They demonstrated that *NOTCH* expression and its activation in mesenchymal stromal cells (MSC) derived from AML contributed to proliferation of AML blasts. Specifically, they could demonstrate that dexamethasone treatment impeded *NOTCH* signaling in these AML-derived MSC, which resulted in reduction of AML blast proliferation. This effect could be validated *in vivo*, with dexamethasone improving survival of AML-bearing mice. These results thus provide a valuable model to better understand the anti-leukemic activity of dexamethasone in AML.

The DEXAML-02 study hypothesizes that the addition of dexamethasone to standard intensive induction chemotherapy may improve the outcome of patients with AML in a prospective, multicenter, single arm phase II trial, as described in this issue of *Haematologica*.¹¹ The investigators of the study, Bertoli *et al.*, established an innovative induction regimen for AML patients over 60 years of age, combining idarubicin, cytarabine, lomustine, and dexamethasone (10 mg twice daily for 3 days). The trial included mostly intermediate- / adverse-risk patients (ELN 2022 criteria) and demonstrated a favorable safety profile, with 60-day mortality of 8% and approximately 20% after three months. The regimen achieved remarkably high response rates: 94% complete response (CR) / CR with incomplete count recovery (Cri) in favorable-risk, 90% in intermediate-risk, and 73% in adverse-risk patients. Notably, 20% of CR/CRI patients underwent allogeneic HSCT after a median of five months and 2 consolidation cycles, with an additional 19% receiving second-line hematopoietic stem cell transplantation (with an overall transplant rate of 39%). Hence, survival outcomes were also promising, with similar event-free survival (EFS) for intermediate- and adverse-risk patients. Multivariate

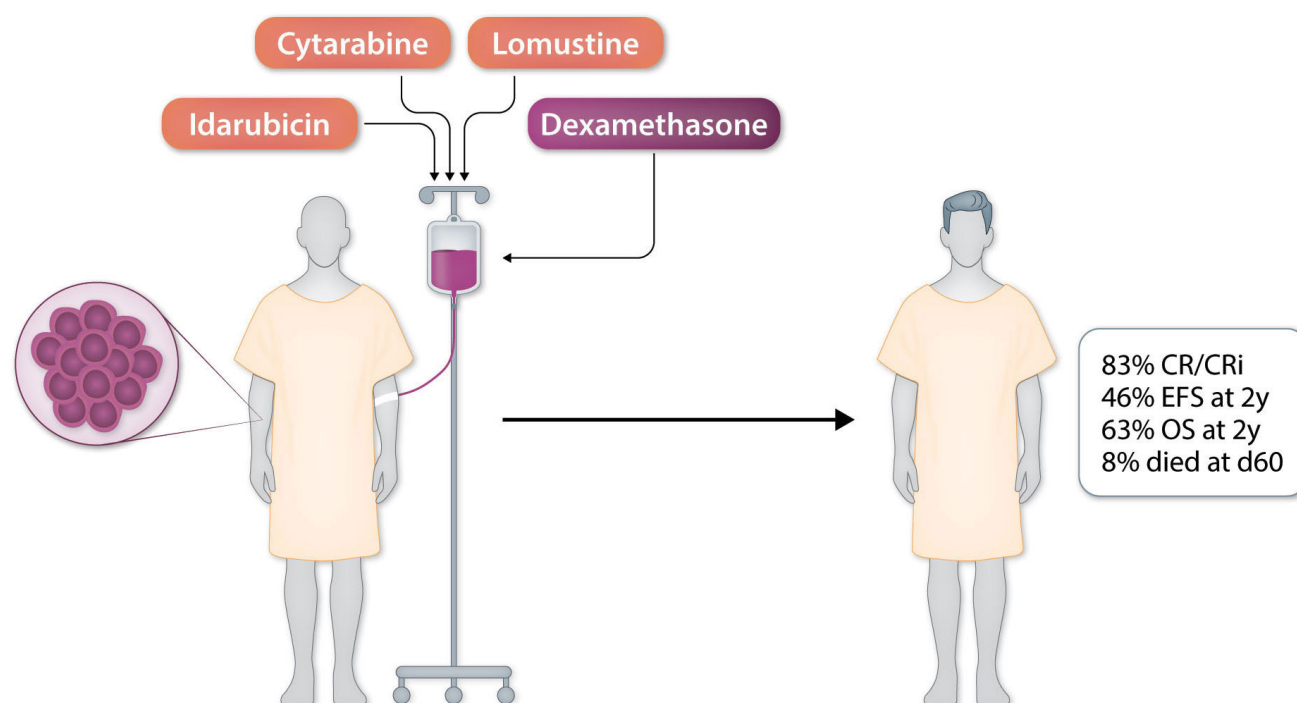


Figure 1. Dexamethasone and lomustine-containing induction regimen in acute myeloid leukemia. CR: complete response; Cri: CR with incomplete count recovery; d: day; EFS: event-free survival; OS: overall survival; y: years.

analysis identified performance status and *NPM1* mutation as predictive for CR. Age and ELN risk predicted EFS, ELN risk predicted also RFS, and performance status and ELN risk predicted overall survival.

The most frequent grade 3–4 adverse event likely to be associated directly with dexamethasone was hyperglycemia (11%) which is generally a well-manageable issue. Another concern could be an increased susceptibility to infections due to steroid-induced immune suppression. The authors reported grade 3–4 infections in 50% of patients, with a 3% rate of septic shock, which is in line with other AML cohorts with similar treatment intensity. The high rate of patients receiving fungal prophylaxis (91%) could be very beneficial in this regard, although the exact rate of fungal infections is not specified.

This well-conducted trial underscores the potential of a dexamethasone “repurposing” in AML treatment, not only for hyperleukocytosis patients but also for patients with lower leukocyte counts. Very encouraging aspects of this work are the favorable safety profile, with no evidence of increased infections. Additionally, dexamethasone is easily available, cost-effective and convenient to use. Certainly, mention

must be made of the fact that the study was designed as a single-arm study and that the applied induction therapy is not the standard of care in many centers. However, the regimen’s efficacy, especially in *NPM1*-mutated patients, warrants further exploration in randomized phase III trials to establish its broader applicability. Beyond implementation in AML induction regimens, the documented safety of this approach also paves the way for expanded use of prompt dosing of newly diagnosed hyperleukocytotic AML patients with dexamethasone, in order to decrease the risk of hyperleukocytosis-related early complications. Indeed, available data^{4,7} suggest that, compared to emergency leukapheresis, dexamethasone may be more efficacious, which implies obvious additional advantages (practicability, cost-effectiveness, etc.) in this life-threatening hematologic emergency setting.

Disclosures

No conflicts of interest to disclose.

Contributions

JDA, JL and ML wrote the manuscript.

References

1. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. *Blood*. 2015;125(21):3246–3252.
2. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417–4423.
3. Würthner JU, Köhler G, Behringer D, Lindemann A, Mertelsmann R, Lübbert M. Leukostasis followed by hemorrhage complicating the initiation of chemotherapy in patients with acute myeloid leukemia and hyperleukocytosis: a clinicopathologic report of four cases. *Cancer*. 1999;85(2):368–374.
4. Stahl M, Shallis RM, Wei W, et al. Management of hyperleukocytosis and impact of leukapheresis among patients with acute myeloid leukemia (AML) on short- and long-term clinical outcomes: a large, retrospective, multicenter, international study. *Leukemia*. 2020;34(12):3149–3160.
5. Largeaud L, Bertoli S, Bérard E, et al. Genomic landscape of hyperleukocytic acute myeloid leukemia.

- Blood Cancer J. 2022;12(1):4.
6. Bertoli S, Picard M, Bérard E, et al. Dexamethasone in hyperleukocytic acute myeloid leukemia. *Haematologica*. 2018;103(6):988-998.
7. Cerrano M, Chevret S, Raffoux E, et al. Benefits of dexamethasone on early outcomes in patients with acute myeloid leukemia with hyperleukocytosis: a propensity score matched analysis. *Ann Hematol*. 2023;102(4):761-768.
8. Issa GC, Stein EM, DiNardo CDD. How I treat: differentiation therapy in acute myeloid leukemia. *Blood*. 2025;145(12):1251-1259.
9. Malani D, Murumägi A, Yadav B, et al. Enhanced sensitivity to glucocorticoids in cytarabine-resistant AML. *Leukemia*. 2017;31(5):1187-1195.
10. Ahmed HMM, Nimmagadda SC, Al-Matary YS, et al. Dexamethasone-mediated inhibition of Notch signalling blocks the interaction of leukaemia and mesenchymal stromal cells. *Br J Haematol*. 2022;196(4):995-1006.
11. Bertoli S, Bérard E, Peterlin P, et al. Dexamethasone added to induction and post-remission therapy in older patients with newly diagnosed acute myeloid leukemia: a multicenter, phase II trial (DEXAML-02). *Haematologica*. 2025;110(10):2475-2480.