Facts about FCE (Fludarabine, Cytarabine, Etoposide) in Acute Myeloid Leukemia

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Contemporary combination chemotherapy regimens induce morphological complete remissions in greater than 80% of younger patients with acute myeloid leukemia (AML) [1]. Approximately half of these patients in first complete remission will eventually suffer disease relapse. Second complete remissions are obtained in more than 50% of relapsing patients but less than 1 in 5 of these patients will be long-term survivors. The outcome of the 10% of AML patients who fail to achieve a complete remission following initial combination chemotherapy is similarly dismal, especially for those patients refractory to high doses of cytarabine [2]. In addition to diminished efficacy, salvage chemotherapy is associated with substantial treatment-related morbidity and early mortality rates ranging between 15 and 20%. Thus, considering the poor clinical outcomes of patients with relapse/refractory AML, improved therapies need to be developed.

In light of these issues, how much enthusiasm should the findings of Aldoss et al. [3] generate? In the manuscript accompanying this editorial, the authors report the clinical outcomes of younger patients with relapsed/refractory AML following treatment with FCE (fludarabine, cytarabine, and etoposide) as salvage therapy. This combination regimen was developed at their institution based on the synergistic preclinical activity between the chemotherapeutic agents and in attempt to spare patients from further anthracycline exposure prior to allogeneic

transplant. The authors describe a high rate of morphological complete remissions (75%) and very low rates of treatment-related morbidity and mortality. Also, half of the patients achieving a complete remission successfully received an allogeneic transplant and pretransplant use of FCE did not increase transplant-related early mortality. Despite these encouraging early outcomes, several concerns remain. The relapse rate after salvage FCE remained high and most patients failed therapy within the first year. This, in turn, translated into a 2-year overall survival rate of <30% with wide confidence intervals, suggesting that the FCE regimen, similar to several other combination strategies, is unable to overcome leukemic chemoresistance in these high-risk patients and, therefore, incapable of positively impacting long-term outcomes.

There are several limitations to this report that need to be highlighted. First, only 20 patients were included in this analysis and there was tremendous heterogeneity on the cohort included in their report. In fact, when patients are allocated to cohorts according to important prognostic factors for relapsed AML (age, duration of first remission, history of allogeneic transplant and karyotype at diagnosis) [4], fewer than 10 patients were included in each cohort. Next, the patients included in this report were treated over a 24-month period and it is not clear from the manuscript how many other patients with relapsed/refractory AML received treatment in their institutions

during that same time. Finally, although all patients received infusional cytarabine and idarubicin (7 + 3 regimen) for induction therapy, it is not clear if patients were deemed refractory after 1 or 2 cycles of therapy. It is also unclear how many consecutive patients received FCE therapy but did not meet the inclusion criteria. These issues combined introduce several potential confounders to the analysis that limit the significance of the findings.

It is, however, important to ask if these outcomes are unexpected or significantly promising when compared to previous reports for this patient population. Over 10 years ago, Leopold and Willemze [5] summarized the results of 29 different studies using combination regimens and reporting the outcomes of patients with relapsed AML. The complete remission rates reported in those studies ranged between 14 and 89%, early mortality ranged from 0 to 32% with a median overall survival of less than 12 months and a probability of 3-year survival

lower than 30%. Similar to that previously reported, age and duration of prior remission were important predictive factors of response to salvage therapy. Collectively, these outcomes are not substantially different to the results described by Aldoss et al. [3].

In summary, FCE appears to be another potentially active regimen in relapsed/refractory AML and it provides an alternative for patients where subsequent use of anthracyclines is contraindicated. However, in the absence of appropriately controlled studies, where study inclusion criteria are harmonized and results of any therapeutic intervention compared to a control group (preferably prospectively), any conclusion regarding the efficacy of FCE is premature. Optimal management for patients with relapse/refractory AML remains a challenge; no salvage treatment regimen has clearly demonstrated improvement in outcomes and new drugs or new combinations of drugs with improved efficacy continue to be needed.

References

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