EDITORIAL

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Targeted therapy in acute myeloid leukemia: aim with caution

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“The concept of a ‘one-size-fits-all’ therapy paradigm may not be the most prudent in a biologically and clinically heterogeneous disorder.”

Acute myeloid leukemia (AML) is a complex disorder. Therapy for AML has been quite diverse over the past 40 years. The most widely accepted induction approach in clinically fit patients, at this time, is treatment with a combination of anthracycline and cytarabine. To date, attempts to improve on this combination have not resulted in significant improvement in overall survival. For patients who are able to achieve a complete remission, risk-adapted consolidation with intensive chemotherapeutic regimens and/or hematopoietic cell transplantation can be offered.

In the induction phase, the issue of the dose intensity of the regimen has been a recent area of focus, particularly for those patients less than or equal to 65 years of age [1–3]. For those patients who are less fit (older than 65 years of age, significant morbidity) and cannot be treated with these aggressive measures, the results are not as encouraging. Realizing that our current therapeutic method is akin to using an atom bomb to treat an insect infestation, recent approaches have looked towards a more precise method. The concept of a ‘one-size-fits-all’ therapy paradigm may

not be the most prudent in a biologically and clinically heterogeneous disorder. So, the question at hand is how intensely to focus the guns of therapy?

To GO or not to GO

Earlier attempts at targeted therapy utilized a myeloid leukemic-specific antibody (anti-CD33), linked to an intercalating agent, calicheamicin (gemtuzumab ozogamicin [GO]). As CD33 is expressed only in myeloid cells, it was felt that this treatment would be very specific, sparing normal cells not expressing the antigen. GO was initially believed to be an effective drug in AML with limited, but well-known side effects, particularly liver toxicity. The NCRI AML 15 trial, a randomized prospective trial of 1115 AML patients, demonstrated the addition of a lower dose of GO to induction, and consolidation therapy produced a significant survival benefit for patients with favorable-risk cytogenetics and a trend for benefit in intermediate-risk patients [4]. Contrary to this trial, a randomized study reported by the SWOG did not demonstrate any value of adding GO to standard induction and maintenance for younger AML patients [5]. The ECOG prospective,

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randomized Phase III trial evaluating the use of GO in an intensive consolidation approach in patients who achieved a complete remission failed to show an improvement in survival [6]. GO has recently been voluntarily withdrawn from the commercial market in the USA.

Tyrosine kinase inhibitor targets

Advances in molecular diagnostics in AML have translated into a significant improvement in our understanding of disease prognosis and biology, and the identification of new targets for therapy [7]. The best described of these are mutations in *FLT3* in cytogenetically normal AML, which occurs in approximately 30% of AML patients. The *FLT3*-internal tandem duplication by constitutively activating cell differentiation and proliferation, and preventing apoptosis has been associated with a shorter remission duration and poorer overall survival [8]. Several tyrosine kinase inhibitors have been used in patients with *FLT3*-positive AML with some success. In a Phase II study, sorafenib (a multikinase inhibitor) was demonstrated to be beneficial in *FLT3*-positive patients [9]. A prospective, randomized trial using midostaurin in conjunction with daunorubicin and cytarabine in induction, consolidation and maintenance will confirm if this approach is feasible. More specific *FLT3* inhibitors, such as AC220, are in the early phases of development; however, the narrower scope of the tyrosine kinase inhibitor may prove not to be as effective, as not all AML cells are addicted to *FLT3* signaling [10]. To date, there is limited clinical information that *FLT3* inhibition improves outcomes in mutation-positive patients; however, the proof of principle should be available in the next year.

Epigenetic targets

Aberrant methylation is another area of recent interest in AML. Several pathways may be involved including the downregulation of tumor suppressor genes and increased CpG methylation. Several of the molecular mutations including *TET2*, *DNMT3A* and *IDH1/IDH2* are associated with epigenetic dysregulation, which occurs in AML [11,12]. *MLL* is another mutation that is associated with hypomethylation of tumor suppressor genes [13].

In particular, for older patients and those with secondary AML, which are well known to have a higher incidence of unfavorable cytogenetics, gene expression and myelodysplastic features,

the use of hypomethylating agents and histone deacetylase inhibitors may be the appropriate type of agents that can be used to complement current therapies. What is encouraging is the fact that, as single agents, these drugs have a relatively benign nonhematologic toxicity profile. Histone deacetylase inhibitors can be paired safely with standard induction of AML patients [14]. There is evidence that the hypomethylating agents are effective in reducing methylation; unfortunately, clinical outcomes thus far still lag behind that of intensive chemotherapy. The use of these agents in the consolidation and maintenance phases might be of benefit for patients who cannot proceed to the intensive consolidation therapy including transplantation.

The future of AML therapy

We are advancing towards an era of personalized medicine in most malignancies, particularly AML. By applying more precise methods during pathologic diagnosis, we can now better identify patients who may benefit from specific therapies. In turn, there is promise of reducing the toxicity of the therapy if certain elements of therapy can be eliminated, reduced or replaced. The key component to being able to implement this approach is the rapid turnaround of the molecular information during the diagnostic phase. Having the information at an earlier time point provides a clearer line of sight to the target. For example, patients with *FLT3*-positive disease may be treated with complementary therapy earlier in the disease, enhancing remissions and outcomes. Patients without cytogenetic study results (due to lack of metaphases) could use the molecular profile to drive decisions [7,8]. As we gather more information using molecular studies, our cannons will be replaced by smart bombs.

From a therapeutic standpoint we have come a long way in AML. Survival is now improved compared with 10 years ago. The one caveat is that our current approaches in AML still use the chemotherapeutic backbone of cytarabine and anthracyclines. We will have to begin to split out subsets of the disease, as has occurred in the treatment of acute promyelocytic leukemia. Realizing that acute promyelocytic leukemia is a distinct entity has allowed us to use less toxic therapies [15]. For now, we should continue treating everyone with a wide scope of therapy, continuing to increase intensity as tolerated. In the near future we can opt to be patient and aim cautiously; as newer diagnostics catch up with

"...as newer diagnostics catch up with the disease, the new acute myeloid leukemia targeted therapies will allow us to hit our mark."

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