Acute myeloid leukemia: introduction to a series highlighting progress and ongoing challenges

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Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and its incidence increases with higher age. Currently, the median age at diagnosis in western countries ranges between 65 to 72 years; in consequence half of the patients with newly diagnosed AML are older than this median and are septua-, octo- or nonagenarians. In the era in which cytostatic chemotherapy, autologous as well as allogeneic hematopoietic cell transplantation were the main pillars of curative treatment approaches, significant improvements in outcome were predominantly restricted to "younger" patients, meaning adult patients younger than 60 years.[1] With the advent of hypomethylating agents,[2,3] a treatment strategy with generally mild side effects and good tolerability became available for older patients, even allowing outpatient administration. Furthermore, hypomethylating agents yielded a small but significant improvement in outcome.[2,3] However, the long-term outcome beyond 2 years was still dismal and not improved by these agents.[2,3] This situation changed meaningfully in 2020 with the introduction of the BCL-2-inhibitor venetoclax in combination with hypomethylating agents.[4] For the first time a substantial proportion of older patients achieved a complete remission either with full or incomplete blood count recovery and, even more importantly, a favorable long-term outcome.[4] Since then, successful treatment and long-term remissions are possible even in octa- and nonagenarians.[5,6] In my own outpatient clinic, it is amazing to see an increasing proportion of septua- and octogenarians for regular 3-monthly follow-up visits in long-term remission after treatment with azacitidine/venetoclax.

This enormous progress was made possible by substantial advances in sequencing technologies leading to rapid advances in understanding the molecular pathogenesis of AML with translation into precision medicine for those patients. This is exemplified by the introduction of targeted treatment approaches with, for instance, *FLT3*, *IDH1/2* and *BCL-2* inhibitors.

Currently, in patients fit for intensive therapy, standard "7+3"-based induction followed by intensive high-dose cytarabine-based consolidation therapy still remains the backbone of the treatment strategy with addition of targeted approaches according to the molecular profile of the disease.[7] However, recent results from large randomized studies showed that the beneficial effect of targeted therapy in combination with intensive chemotherapy may be restricted to younger patients (aged ≤60 years) (Erba *et al.*; unpublished data).[8] In both studies, patients older than 60 years suffered from increased toxicity with fatal outcomes when targeted therapy was added to standard intensive induction therapy. This raises a couple of questions. On the one hand, should we redefine the criteria to classify a patient as *fit for intensive therapy* on the background of these new combination approaches? On the other hand, could non-intensive approaches based on azacitidine/venetoclax be as effective as intensive chemotherapy in younger patients as well? Despite significant advances in biological insights, targeted therapies, and prolonged survival for most AML patients, important questions remain unresolved.

This issue of *Haematologica* contains a timely series on AML, with four comprehensive papers presented by experts in the field. The authors provide an update on where the field is going in terms of new data and new perspectives, while also outlining remaining challenges.

In the first paper[9] Sabine Kayser and Mark Levis summarize the current knowledge of the molecular landscape of AML, focusing particularly on the utility of molecular markers in prognostication and treatment decision-making in AML. The second paper[10] broadens the view on AML biology with an emphasis on therapy-resistant cells harboring stem cell properties. In this paper Patrick Stelmach and Andreas Trumpp highlight the concept of leukemic stem cells and their important phenotypic and epigenetic plasticity in response to therapy-induced stress, which results in various mechanisms mediating treatment resistance.

The two remaining papers[11,12] deal with translation of current knowledge into treatment algorithms. Sonia Jaramillo and I give an overview of the current treatment landscape for adult AML (excluding allogeneic hematopoietic cell transplantation), concentrating on the discourse for whom and when to use intensive or non-intensive approaches.[11] Finally, Mohamad Mohty's group focuses on allogeneic hematopoietic cell transplantation and the role of new drugs before, during and after transplantation.[12] In this review it is apparent that the previously largely dichotomized treatment worlds, transplant specialists and leukemia doctors, are moving closer together.[12]

When reading these reviews side-by-side, it becomes clear that enormous progress has been achieved in roughly the last decade.[1] Furthermore, the ways to move forward in all fields are well illustrated in the papers, allowing the reader to envision what the next review series on AML in *Haematologica* will look like in a couple of years.

Disclosures

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