Chasing quality remission in acute myeloid leukemia: intensity of induction and residual disease

Yishai Ofran

Department of Hematology and Stem Cell Transplantation, Shaare Zedek Medical Center and the Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

E-mail: yofran@szmc.org.il

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TITLE	Improving the remission quality in acute myelogenous leukemia (AML) by increasing cytoreduction during induction therapy.
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Induction of remission is the first and ultimate goal in the treatment of patients with acute myeloid leukemia (AML). Ever since cure became achievable in AML, remission has been recognized as essential to successful treatment. However, for many years, toxicity associated with intensive chemotherapy limited doctors' willingness to increase chemotherapy doses. In addition, as long as light microscopy was the only tool for marrow evaluation and mini-

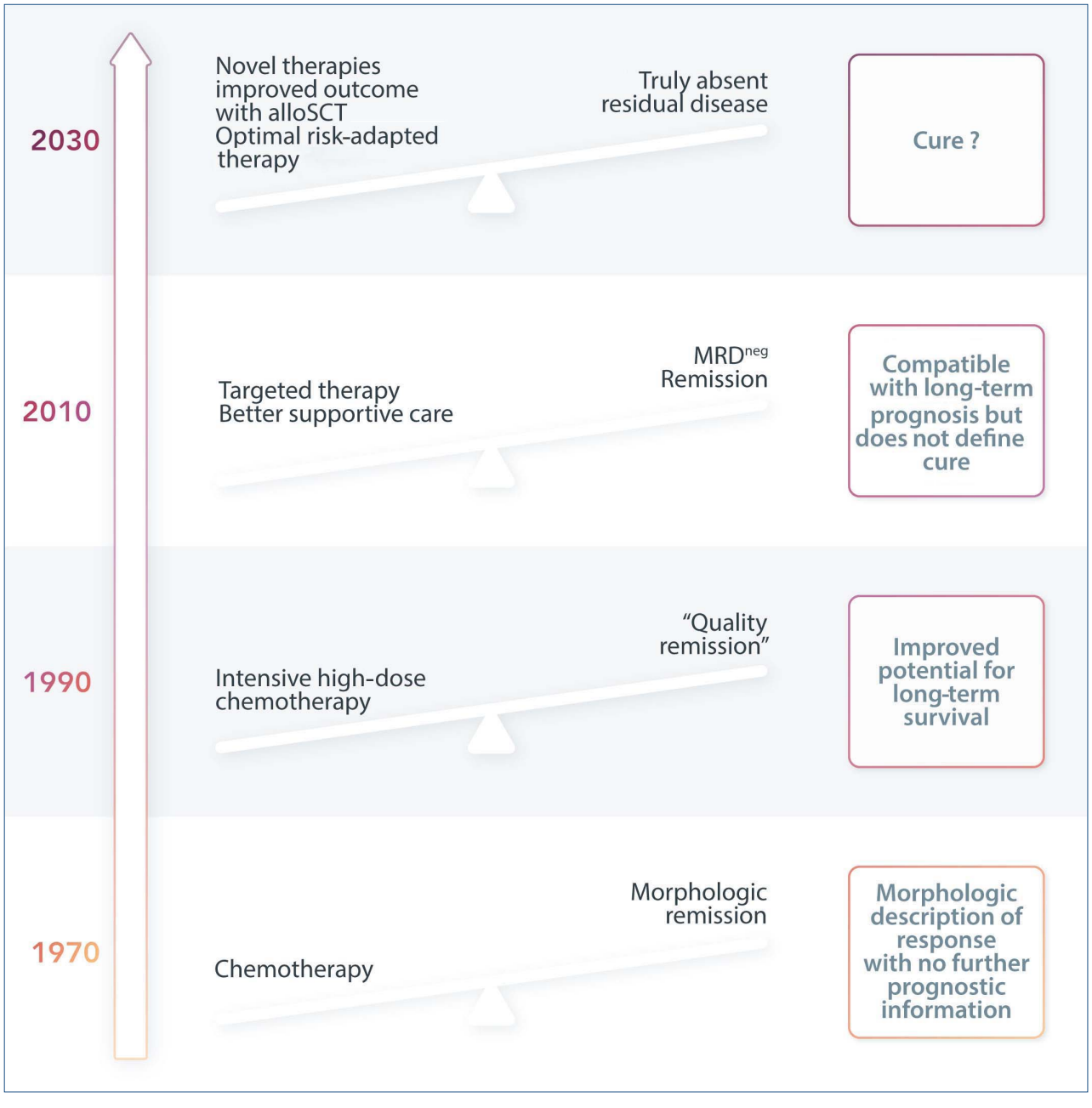

Figure 1. History and future direction of treatment/response evaluation in acute myeloid leukemia. The way we evaluate response to induction therapy in acute myeloid leukemia patients has been modified in the last 50 years. Dr. Arlin's vision regarding the need to achieve "quality remission" had developed when molecular techniques allowed measurement of minimal residual disease. The accumulation of novel therapeutic agents in parallel with better understanding of leukemia biology drives improved patient outcome and potential cure. alloSCT: allogeneic stem cell transplant; MRD: minimal residual disease.

mal residual leukemia could not be measured, relapse after the achievement of morphologic remission was unpredictable. Back in the 1990s, the late Dr. Zalman Arlin was seeking ways to improve the quality of remission. Arguing that presence of unrecognized minimal residual disease (blasts that survived the induction regimen) represents the seeds of relapsed disease, he championed for the potential benefit of intensifying induction regimens, believing that this would result in a deeper or, as he called it, "quality remission". The rationale was that susceptibility of cycling leukemia cells to the toxic effects of chemotherapy is dose-dependent, while normal hematopoietic stem cells are "dormant" and relatively protected from chemotherapy.

A similar protocol had previously been demonstrated to be effective by Dr. Arlin in acute lymphoblastic leukemia patients. To prove this concept in AML, Dr. Arlin launched a clinical trial exploring induction with higher doses of chemotherapy. Induction included five days of cytarabine 3 g/m^2 over 3 hours, mitoxantrone 80 mg/m^2 on either day 2 or 3 (as opposed to the usual approach of dividing such a dose over 5-6 days), and varying doses of etoposide (VP-16), ranging from 50 to 150 mg/m^2 on days 1, 3, and 5. Tragically, after a short illness, Dr. Arlin, succumbed to a brain tumor at the age of 47, and only preliminary results of 19 AML patients (10 newly diagnosed and 9 with relapse) were published under his name as a conference paper.[1]

This landmark work proved the feasibility and potential benefit of an intensified induction regimen. Final results of this regimen as a phase II study were published a few years later, demonstrating that with such an intensive regimen remission can be achieved in 36/45 (80%) of newly diagnosed young AML patients with acceptable toxicity.[2] The demonstration that intensification of induction is feasible and is potentially beneficial was later confirmed by phase III studies of intensified daunorubicin.[3,4] This concept also paved the way for combination therapies as induction (such as adding midostaurin or gemtuzumab ozogamicin to standard induction) and sequential therapy for resistant AML.[5]

Dr. Arlin's hypothesis that not all remissions are alike, and undetectable MRD is what needs to be eradicated, is now well established. The search for "quality remission" is today known as MRD eradication, and major efforts are being made to measure, monitor and eliminate disease remnants (Figure 1). Current practice and guidelines of therapy in AML incorporate sensitive molecular techniques developed after Dr. Arlin had passed away, but his memory lives on as a visionary clinical scientist who saw beyond his time and was active in the search for major breakthroughs to improve AML therapy.

Disclosure

No conflicts of interest to disclose.

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