Genetics as predictive marker for consolidation therapy with high-dose cytarabine in acute myeloid leukemia

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TITLE	Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype.
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High-dose cytarabine was established as the major component of consolidation chemotherapy in acute myeloid leukemia (AML) by the randomized study performed by the prestigious US Cancer and Leukemia Study Group B. The trial recruited between 1985 and 1990 and was published by Robert J. Mayer and colleagues in 1994 in the *New England Journal of Medicine*.[1] This study established the concept of a dose-response effect for cytarabine (100 mg *vs*. 400 mg *vs*. 3 g) in younger patients with AML in first complete remission. However, although disease-free

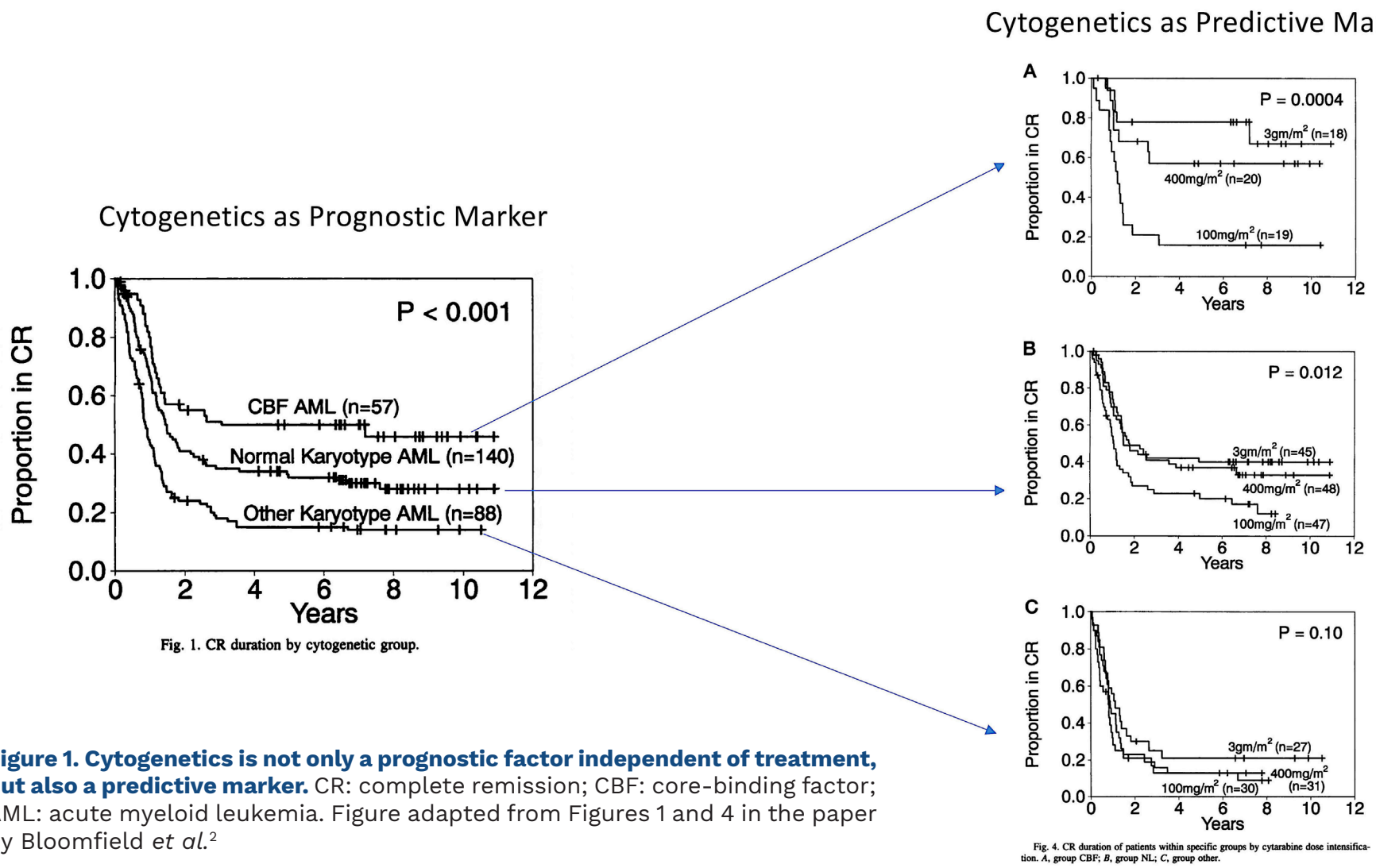

Figure 1. Cytogenetics is not only a prognostic factor independent of treatment, but also a predictive marker. CR: complete remission; CBF: core-binding factor; AML: acute myeloid leukemia. Figure adapted from Figures 1 and 4 in the paper by Bloomfield *et al.*[2]

survival after 4 years was improved from 24% in the 100 mg group, to 29% in the 400 mg group and to 44% in the 3 g group not all patients benefited equally from dose-intensification.

At this point, the companion genetic diagnostics study including patients with adequate, pretreatment, centrally reviewed cytogenetics came into focus.[2] It was already clear that cytogenetics was one of the major prognostic markers, identifying better outcome in AML patients with so-called core binding factor (CBF) abnormalities [t(8;21)(q22;q22) and inv(16)(p13q22) or t(16;16)(p13;q22)] and those exhibiting a normal karyotype.[3] However, for the first time it was possible to show that cytogenetics is not only a prognostic factor independent of treatment, but also a predictive marker indicating better efficacy of high-dose cytarabine as consolidation therapy in distinct genetically defined subgroups (Figure 1).

From different perspectives the study published in 1998 by Clara D. Bloomfield was a pivotal study: (i) it set the standard for consolidation therapy in AML patients with CBF abnormalities;[4,5] (ii) it demonstrated impressively how companion diagnostics can guide results from randomized clinical trials; and (iii) it paved the way for the design of modern clinical trials - particularly with respect to biobanking, long-term follow-up and patient-reported outcomes - to allow maximal gain of knowledge through a multidimensional approach.

Disclosures

No conflicts of interest to disclose.

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