

## TOWARDS AN INCREASINGLY MOLECULAR-BASED, PATIENT-ORIENTED TREATMENT OF ACUTE MYELOID LEUKEMIA

In recent years several leukemia-specific cytogenetic abnormalities have been identified and the related molecular lesions characterized.<sup>1</sup> These include, among others: t(15;17) (q23;q21) with PML/RAR $\alpha$  fusion gene; t(8;21) (q22;q22) with AML1/ETO chimeric gene; inv(16) with CBFb/MYH11 hybrid gene; 11q23 translocations with MLL gene lesions, and t(5;9)(q21;q28) with DEK/CAN chimeric gene. Studies of late suggest that cytogenetic and molecular information may be useful in therapeutic decision making.

Among AML subtypes, the most peculiar entity is undoubtedly acute promyelocytic leukemia (APL). In their excellent review in this journal, Diverio *et al.*<sup>2</sup> concluded that the PML/RAR $\alpha$  hybrid gene is both crucial for the pathogenesis of APL and a specific tumor marker. In fact, it is rapidly detectable by reverse transcriptase-polymerase chain reaction (RT-PCR) in the RNA extracted from leukemic blasts and is found in 100% of APLs. Lo Coco *et al.*<sup>3</sup> have recently reported at the ASM meeting that 94% of patients with PML/RAR $\alpha$ -rearranged APL achieve hematological complete remission (CR) with oral all-trans-retinoic acid (ATRA) and idarubicin (the so-called AIDA regimen). No case of resistant leukemia was observed in this GIMEMA-AIEOP trial and 61% of patients achieving CR were PCR negative following induction therapy, before consolidation. These remarkable results must be compared with those of a recent American phase-III randomized study of ATRA vs daunorubicin and cytarabine as APL induction therapy.<sup>3</sup> The CR rate was 67% in each arm, about 2/3 of that obtained in the Italian trial. There is no question that at present the best induction therapy by far for APL patients is a combination ATRA and idarubicin. This raises the question of routinely employing RT-PCR to detect the PML/RAR $\alpha$  hybrid gene in cases with borderline morphology in order to properly guide

induction therapy. Finally, as shown by Diverio *et al.*,<sup>2</sup> all studies reported till now on PCR monitoring in APL have documented that identification of small amounts of residual disease at remission strongly predicts impending relapse.

Other AML patients undergo remission induction therapy with a classical "3+7" scheme, or the recently developed ICE regimen.<sup>4</sup> Sixty to 80% of them are expected to achieve complete remission; the subsequent clinical course correlates at least in part with the molecular lesion.

The two most prevalent cytogenetic abnormalities encountered in AML, t(8;21)(q22;q22) and inv(16), accounting for about one third of the karyotypic abnormalities found in *de novo* AML, apparently result in the same molecular event, i.e. disruption of the transcription factor complex AML1-CBF $\beta$ .<sup>1</sup> RT-PCR analysis of the AML1/ETO fusion transcript can be employed to confirm eradication of the leukemic clone in AML patients with t(8;21)(q22;q22).<sup>5</sup> The available evidence suggests that AML patients with t(8;21)(q22;q22) and inv(16) have a good prognosis and may experience long-term remission (and possibly be cured) with intensive postremission chemotherapy based on high-dose Ara C.<sup>1</sup>

The remaining AML patients are at very high risk of relapse. Those aged 55 or less with an HLA-identical sibling should undergo allogeneic bone marrow transplantation. The others up to age 65 should receive autologous stem cell transplantation. In this issue, Aglietta *et al.* review the available data on peripheral stem cell transplantation in AML.<sup>7</sup> The preliminary experience of the Institute of Hematology Seragnoli, University of Bologna School of Medicine, looks very promising. Should these data be confirmed in ongoing prospective studies, peripheral stem cell transplantation could become an effective intensive post-induction therapy for many AML patients. Operative guidelines for hematologists interested in this

subject are provided in the above review, while further information on CD34-positive cells can be found in a previous article in this journal.<sup>8</sup>

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### References

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