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Leukemia stem cell candidates in acute myeloid leukemia predict refractoriness to conventional chemotherapy and adverse clinical outcome
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We have shown that leukemia stem cells candidates (LSCC) can be prospectively identified by high activity of aldehyde dehydrogenase (ALDHbr) among the leukemia blasts from the marrow of patients with acute myeloid leukemia (AML). These LSCC demonstrated functional characteristics of stem cells in vitro and in xenogenic transplantation models.

Methods: In this report we have studied the relationship between the frequency of LSCC at diagnosis with persistence of leukemia blasts after induction chemotherapy as well as with long-term clinical outcome. We have identified subsets among the LSCC and correlated their individual functional properties with the corresponding marker profile using single cell sorting.

Results: The percentage of LSCC (ALDHbr) in 101 patients with AML ranged from 0.01% to 12.90% with a median of 0.51%. Frequencies of LSCC among the leukemia blasts at diagnosis correlated significantly with the persistence of leukemia after the first induction chemotherapy (n=79, Spearman R=0.7797, P<0.0001). During the observation period of 24 months, 21 of 60 patients with high levels of LSCC died as compared to 7 of 41 patients with low levels of LSCC (p=0.029). The overall survival (OS) probability for the patients with high levels of LSCC was significantly worse (p=0.05) than in those with low LSCC. Characterization of these LSCC at a single cell level showed that a varying proportion, i.e. 15% to 78% of their progeny cells demonstrated the same chromosomal aberrations as the original leukemia population, indicating the presence of normal HSC among our preparation of LSCC. The LSCC were more resistant to chemotherapy as compared to the other leukemia blasts and co-culture with MSC further increased the resistance of the ALDHbr cells against chemotherapy (n=3, p<0.001).

Conclusions: Thus high frequencies of LSCC at the time of diagnosis predict persistence of leukemia blasts, failure to achieve CR within the first cycle and poor overall clinical outcome and hence represent an independent poor prognostic factor.