Risk-adapted treatment of myelodysplastic syndromes

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Myelodysplastic syndromes are clonal disorders of hematopoietic stem cells with a propensity to evolve into acute myeloid leukemia. The World Health Organization (WHO) classification of myeloid neoplasms is a very useful tool for defining the different subtypes of these disorders. The WHO variants show impressive clinical heterogeneity, ranging from conditions with a near-normal standardized mortality ratio to entities that are very close to acute myeloid leukemia. Retrospective [Malcovati et al, J Clin Oncol. 2005 Oct 20; 23 (30): 7594-603] and prospective [Germing et al, Haematologica. 2006 Dec; 91 (12): 1596-604] studies have shown that the WHO classification is feasible, provides valuable prognostic information, and is useful for clinical decision making. One of the novel WHO variants, the myelodysplastic syndrome with isolated del(5q), has been found to have a peculiar molecular basis (haploinsufficiency of genes located at 5q31-q32) and a remarkable response to lenalidomide. After showing that dependency on transfusions has an effect on the likelihood of survival [Cazzola & Malcovati, N Engl J Med. 2005 Feb 10; 352 (6): 536-8], we studied the most significant prognostic factors in myelodysplastic syndromes taking into account both their values at clinical onset and their changes in time, with the aim of developing a dynamic model for predicting survival and leukemic evolution that can be applied at any time during the course of the disease [Malcovati et al, J Clin Oncol. 2007 Aug 10; 25 (23): 3503-10]. The most important variables for the prognostic model were WHO subgroups, karyotype, and transfusion requirement, and based on these parameters we defined a WHO classification-based prognostic scoring system (WPSS). In the learning Pavia cohort, WPSS was able to classify patients into five risk groups showing different survivals (median survival from 12 to 103 months) and probabilities of leukemic evolution. WPSS was shown to predict survival and leukemia progression at any time during follow-up, and its prognostic value was confirmed in the Duesseldorf validation cohort. More recently we found that bone marrow fibrosis represents an additional independent prognostic factor, as this feature identifies a distinct clinical entity characterized by high transfusion need and poor prognosis. A risk-adapted treatment strategy is mandatory for disorders that range from indolent conditions lasting years to forms approaching acute myeloid leukemia. The approach to a patient with myelodysplastic syndrome should begin with a period of observation to assess the rate of progression, if any. Patients at very low risk of leukemic evolution and without any transfusion requirement can just be followed. At present, the only treatment that can definitely prolong survival is allogeneic hematopoietic stem-cell transplantation, but only a minority of patients with myelodysplastic syndrome are eligible for such treatment and have a donor. According to a decision analysis [Blood. 2004 Jul 15; 104 (2): 579-85] transplantation should be delayed in low risk patients, while it should be performed soon in individuals at high risk of leukemic progression. The remaining potentially effective treatments include erythropoietin alone or in combination with granulocyte colony-stimulating factor, lenalidomide, immunosuppression with antithymocyte globulin and / or cyclosporine, hypomethylating agents (azacitidine and decitabine), and intensive chemotherapy. Despite recent progress, red-cell transfusions and iron chelation remain the mainstays of therapy in many patients with myelodysplastic syndrome.