inside blood

Leukemic cell resistance: targeting needed beyond MDR-1

Multiple risk factors exist for prognosis and response to therapy in acute myeloid leukemia (AML). These features include patient's age, performance status, presenting leukocyte count, marrow cytogenetics, blastic morphology (dysplasia), immunophenotype and oncoprotein (proapoptotic and antiapoptotic oncogene) expression, molecular phenotype (flt3 expression), and multidrug resistance (MDR) mechanisms. Many poor-risk parameters are interrelated, including the association between (1) increased age, immature stem cell phenotype, and MDR expression, (2) flt3 expression, nonpoor-risk cytogenetics, and elevated leukocyte count, and (3) independence between resistance to apoptosis (decreased bax/bcl2 ratio) and MDR expression (Leith et al, Blood. 1997;89:3323-3329; Wuchter et al, Leukemia. 1999;13:1943-1953; Pallis et al, Br J Haematol. 2003;120:1009-1016).

Blasts from a high proportion of AML patients overexpress the *MDR-1* gene (coding for the p170 glycoprotein, Pgp), with their cells being relatively resistant to several antileukemic drugs by extruding them through an energy-dependent pump. Agents capable of modulating MDR-1 have been used for treating poor-risk AML including quinine, tamoxifen, calcium channel blockers, cyclosporine A, and its analog, PSC833. These drugs decrease MDR-1 function as measured by blocking rhodamine-123 efflux. However, numerous other mechanisms in addition to MDR-1 overexpression also enhance resistance of leukemic cells to chemotherapy (Sikic, Semin Hemat. 1997;34[suppl 5]:40-47). These mechanisms include extracellular (eg, drug pharmacokinetics, distribution) or intracellular derangements. The intracellular drug resistance mechanisms include abnormal transmembrane transport, decreased drug detoxification, altered nuclear targets, and apoptotic resistance. In addition to Pgp, overexpression of other potentially relevant members of the transport protein superfamily that extrude cytotoxic drugs include the MDR-related protein (MRP1) and lung-related protein (LRP).

Variable clinical results (predominantly negative in phase 3 studies), often using cyclosporin or PSC833 plus chemotherapy, have been reported with MDR-1 modulator trials in adult patients with AML (Greenberg et al, Blood. 1999;94[suppl 1]:383a; Baer et al, Blood. 2002;100:1224-1232). The phase 3 clinical trial reported by Solary and colleagues for the French AML study group in this issue (page 1202) provides results of this group's use of quinine as an MDR-1–modulating agent plus chemotherapy in relatively young patients (< 61 years) with de novo AML. Although an increased response rate was found for MDR-1–positive patients, neither the overall response rates nor patient survival were influenced by this agent. The lack of clinical benefit in this study differed from this group's prior positive report using similar therapy for treating myelodysplastic syndrome (MDS) and AML post-MDS patients (Wattel et al, Brit J Haematol. 1998;102:1015-1024). This differing responsiveness in AML may relate to patient selection, as the MDS patients were older, with more immature stem cells having a higher proportion of potentially susceptible blasts expressing MDR-1.

The limited clinical efficacy in this and other modulator trials likely relates to the multiple alternate resistance mechanisms in AML—beyond MDR-1. Future studies will need to more clearly define the nature and heterogeneity of blast cell resistance mechanisms in AML and attempt to target these lesions more comprehensively than with the single modulatory agent approaches currently being used.

—Peter Greenberg
Stanford Medical Center and
VA Palo Alto Health Care System

Chronic graft-versus-host disease (cGVHD) is more frequent due to changes in the practice of stem cell transplantation (SCT)

The use of alternative donors, the use of peripheral blood (PB) instead of bone marrow (BM) as the stem cell source, increasing upper age limit, the use of donor lymphocyte infusions (DLIs) to treat relapse and conversion to total donor chimerism, and the use of nonmyeloablative transplants (where DLI is frequently given) have all contributed to the increase in cGVHD. cGVHD is associated with decreased quality of life, impaired functional status, and increased risk of nonrelapse mortality and morbidity (reviewed in Lee et al, Biol Blood Marrow Transplant. 2003;9:215-233). A recent randomized study found that patients receiving PB allogeneic transplants had more refractory cGVHD, requiring more courses of therapy than patients receiving BM transplants (Flowers et al, Blood. 2002;100:415-419). This finding, coupled with the randomized trial showing that the addition of cyclosporine to prednisone did not increase the response rate in newly diagnosed patients, has made finding effective therapies for cGVHD imperative (Koc et al, Blood. 2002;100:48-51).

In this issue of *Blood*, Seaton and colleagues report on 28 patients receiving extracorporeal photopheresis (ECP) for refractory biopsy–proven cGVHD (page 1217). Responses were scored using quantifiable variables, including extent and severity of skin involvement, liver function tests, blood counts, and pulmonary function tests. After 6 months of ECP, median skin scores were 53% lower ($P = .003$). The authors also studied predictive factors for response. ECP is not an easy treatment option for many patients with chronic GVHD. They must have reasonable access (financial and geographic) to a center offering ECP. ECP is