Developmental Therapeutics for Myelodysplastic Syndromes

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Abstract
The management strategy for patients with myelodysplastic syndromes (MDS) has evolved from sole reliance on supportive measures to active treatment guided by disease risks. Recent progress in understanding the molecular pathogenesis of MDS has accelerated the discovery of new therapeutic targets, and consequently launched the development of several novel therapeutics that are currently in varied stages of clinical testing. One such agent is lenalidomide, which has shown remarkable effectiveness in the cytogenetically defined subset of MDS with the chromosome 5q31 deletion. The advent of new and effective targeted therapeutics may beneficially affect outcomes of an ever-increasing number of patients with MDS. This discussion summarizes the preliminary results of selected novel therapeutics. (JNCCN 2006;4:78–82)

Researchers developed new therapeutic strategies for myelodysplastic syndromes (MDS) after refinements in the characterization of the disease and its natural history. The World Health Organization refined the classification of MDS by incorporating morphologic and cytogenetic features with greater discriminatory power.\(^1\) Complemented by the routine application of the International Prognostic Scoring System,\(^2\) these recent adaptations provided the foundation for universal measures of therapeutic response created by an International Working Group.\(^3\) This article summarizes novel, non-cytokine therapeutics under development for MDS, categorized by pharmacologic class and intended biologic target (Table 1). Hypomethylation agents capable of epigenetic alteration in MDS are discussed elsewhere in this issue.

Immunosuppressive Therapy
In selected cases, ineffective hematopoiesis may arise through hematopoietic inhibitory immune response, a pathobiology that overlaps with aplastic anemia. Treatment with either cyclosporine or antithymocyte globulin can yield a high frequency of response in appropriately selected candidates with lower-risk disease.\(^4\) Barrett et al.\(^7\) updated the National Institutes of Health experience with a study of 60 patients with MDS, showing that one third of patients with less than 15% blasts became independent of red blood cell (RBC) transfusions and 87% of responders remained free of progression at 2.5 years. Multivariate analysis identified only HLA-DR15 allele, younger age (< 60 years), and shorter duration of RBC transfusion dependence as independent variables that may be applied in a predictive model for response estimation.\(^8\) Given the inherent risk for infection in immunosuppressive therapy, proper selection of candidates is paramount.

Cytoprotective Therapy
In vitro neutralization of tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)) enhances the outgrowth of hematopoietic progenitors in MDS.\(^9\) Reports of hematologic improvement in selected patients with high endogenous TNF-\(\alpha\) plasma concentrations treated with a TNF-selective antagonist provided the first evidence that this strategy may have clinical benefit in MDS. Two patients with low- and intermediate-1–risk MDS experienced major and minor
erythroid responses, respectively, after treatment with the chimeric monoclonal anti-TNF-α antibody infliximab, which was associated with a significant reduction in the percentage of apoptotic marrow precursors.10

Organic thiols, such as glutathione, the most abundant cellular thiol, represent the primary cellular defense against oxygen free radicals. Trials combining amifostine with erythropoietin have yielded conflicting results, indicating that this approach offers only marginal benefit as monotherapy.11,12

### Antiangiogenic and Antiapoptotic Therapy

Vascular endothelial growth factor-A (VEGF-A) production by myelomonocytic precursors has been implicated in the generation of medullary neovascularity in MDS; autocrine and paracrine stimulation of receptor-competent myeloblasts; and ineffective hematopoiesis in receptor-naïve progenitors through the paracrine induction of inflammatory cytokines.13 Based on these findings, antiangiogenic molecules have emerged as a promising class of therapeutics for MDS, with their principal impact on erythropoiesis.

### Thalidomide

Thalidomide, which possesses antiangiogenic and TNF-α inhibitory properties, was the first agent in this class to be evaluated in MDS. In a phase II trial performed at the Rush Presbyterian Cancer Institute,14 19% of patients (16/83) responded, with 15 patients experiencing an erythroid response. Researchers administered a median dose of 150 mg/d of thalidomide. Dose-limiting adverse effects included fatigue (79%) and constipation (71%), followed by dyspnea (54%) and fluid retention. The North Central Cancer Treatment group evaluated a more aggressive dose-escalation schema (200–1,000 mg/d), showing excessive early attrition caused by excess toxicity after a median interval of 2.5 months or less.15 The results are expected soon of a national Celgene-sponsored, randomized, placebo-controlled phase III trial, completed in the fall of 2003, that evaluated the frequency of major erythroid response with low-dose thalidomide.

### Lenalidomide

Clinical studies recently began involving thalidomide analogues with improved toxicity profiles. Lenalidomide (CC-5013) is a 4-amino-glutarimide derivative of thalidomide that lacks the neurologic toxicities of thalidomide, yet is a potent modulator of ligand-induced cellular responses, including potentiation of antigen-induced immune response, suppression of angiogenic response, and potentiation of erythropoietin signaling. In a phase I/II study, 43 patients who had either undergone failed treatment with recombinant erythropoietin or had high endogenous erythropoietin level and transfusion burden were treated in sequential cohorts with lenalidomide doses of 25 or 10 mg/d, or 10 mg/d for 21 days of every 28-day cycle.16 After 16 weeks, the researchers assessed erythroid response, which was the primary endpoint. Twenty-four patients experienced response (56%), with 21 major responses, including sustained transfusion independence (n = 20) or a rise in hemoglobin more than 2 g/dL (n = 1). Patients with a clonal interstitial deletion involving chromosome 5q31 (83%) had the highest response rate compared with patients with a normal or alternate karyotype (45%). The most common adverse events were dose-dependent neutropenia and thrombocytopenia that were manageable with treatment interruption or dose reduction.

In a recently completed multicenter phase II study restricted to patients with lower-risk, transfusion-
dependent MDS with the 5q31.1 deletion (MDS-003), 75% of patients treated with lenalidomide experienced an erythroid response in an intent-to-treat analysis, with 66% of patients experiencing sustained RBC transfusion independence. Of 115 patients eligible for evaluation, 81 (70%) experienced cytogenetic responses by 24 weeks, including complete cytogenetic responses in 44% of patients. Erythroid responses were durable, with the median duration of transfusion independence not reached at a median of 58 weeks follow-up as of March 31, 2005. Cytogenetic and erythroid response appeared independent of karyotype complexity. The results of the trial are under review by the U.S. Food and Drug Administration, and if approved, lenalidomide is expected to become a primary therapy for patients with this specific cytogenetic abnormality.

**Arsenic Trioxide**

Arsenic trioxide covalently binds and depletes sulfhydryl-rich proteins, such as glutathione, to induce apoptosis and suppress angiogenic response. Preliminary results of 3 phase II trials indicate that arsenic trioxide monotherapy has modest activity in lower- and higher-risk MDS, with its predominant activity on the erythropoiesis. Combination therapy trials have begun.

**Bevacizumab**

Other investigated antiangiogenic agents either have shown a more limited toxicity-benefit profile for extended use or have not yet completed clinical investigation. Bevacizumab, a recombinant humanized monoclonal antibody that neutralizes VEGF-A in vivo is currently completing phase I investigation in MDS but has shown modest hematologic activity largely restricted to erythropoietic improvement.

**Receptor Tyrosine Kinase Inhibitors**

Small molecule inhibitors of the VEGF receptor tyrosine kinases (RTK) have had limited investigation in MDS. The RTK inhibitors have broad kinase activity that extends to other type III receptors, such as those corresponding to the platelet-derived growth factor receptor-β (PDGFRβ), FLT3, and c-kit ligands. SU5416 is the first agent in its class to complete phase II investigation. Despite an increase in apoptotic index in the myeloblast population, the multicenter trial involving patients with higher-risk MDS and acute myeloid leukemia (AML) showed minimal impact on leukemia burden. Clinical investigation of the orally bioavailable analogue SU11248 in patients with AML ended prematurely because of limiting nonhematologic organ toxicities. A multicenter trial involving patients with advanced MDS and AML showed only minimal activity using a twice-daily dosing schedule of a second oral RTK inhibitor, PTK787. The Cancer and Leukemia Group B is currently investigating PTK787 in a single daily dose in patients with lower-risk MDS.

**Imatinib**

Constitutive ras and mitogen-activated protein kinase (MAPK) activation occurs in 40% to 60% of chronic myelomonocytic leukemia (CMML) cases, resulting from either activating mutations within ras alleles or reciprocal translocations deregulating RTKs. Imatinib has emerged as the treatment of choice for patients with CMML harboring translocations involving the PDGFRβ locus at chromosome 5q33. Imatinib binds to the adenosine triphosphate-binding pocket of the PDGFRβ analogous to its interaction with BCR/ABL to inhibit kinase activity. Cases indicate that imatinib monotherapy yields rapid hematologic control with durable cytogenetic remissions. SCIO-469 is a promising new antiapoptotic agent that targets hematopoietic progenitors and the microenvironment. This small molecule inhibits p38-α MAPK, a convergence point for signaling by inhibitory cytokines such as TNF-α, interferon gamma, and transforming growth factor β, and death receptor activation of the apoptotic response. A phase I/II clinical study with this oral agent is in progress.

**Farnesyl Transferase Inhibitors**

Activating point mutations of the ras proto-oncogene are detected in less than 20% of unselected patients with MDS but are common in CMML. The ras gene superfamily encodes guanosine triphosphate hydro- lases (GTPases) that serve as critical regulatory elements in signal transduction, cellular proliferation, and maintenance of the malignant phenotype. Farnesylation of carboxy-terminal consensus sequences by farnesyl protein transferase is the rate-limiting post-translational modification of Ras GTPases that is requisite for membrane association and activity. The farnesyl transferase inhibitors (FTIs) represent a novel class of oral inhibitors of Ras and other prenylation-dependent proteins.

Tipifarnib (R115777) and lonafarnib (SCH66336) are the leading non-peptide, heterocyclic oral FTIs
for which phase I and II clinical studies have been completed, primarily in higher-risk MDS. Preliminary results indicate that this class of agents is active, yielding pathologic and hematologic improvement in 30% to 40% of patients. An unexpected finding in the lonafarnib studies was the induction of leukocytosis, particularly in patients with proliferative CMML (≥12,000/mL white blood cell count), necessitating close monitoring of patients receiving FTI treatment for early introduction of cytoreductive therapy.

Pharmacologic Differentiators

The inability to identify relevant biologic targets whose activity can be modified by synthetic small molecules has limited the development of pharmacologic agents that can induce hematopoietic differentiation in MDS. TLK199, a novel liposomal glutathione derivative that promotes granulopoiesis in preclinical models, recently completed phase I investigation in MDS. Glutathione S-transferase P1-1 (GST P1-1) is a negative regulator of C-Jun NH2-terminal Kinase (JNK), which suppresses the proliferation and differentiation of myeloid precursors. TLK199 is de-esterified intracellularly to the active diacid form, TLK117, which inhibits GST P1-1 to relieve inhibition of the MAPK pathway. Preliminary results of the initial trial have shown hematologic improvement in 2 or more lineages in 6 of 21 patients who could be evaluated. Investigations with this agent will continue with an orally bioavailable analogue.

Conclusions

Progress in the characterization of MDS has enabled the application of new prognostic models to guide therapeutic goals. The advent of novel and effective target-selective therapeutics has raised expectations that the approach to managing these disorders has changed forever. Participation in clinical trials is essential to ensure further therapeutic progress, particularly for individuals with low probability of response to standard therapy.

References


