The myelodysplastic syndromes (MDS) can be divided into “early” and “advanced” disease by evaluation of prognostic variables such as the number of cytopenias, karyotype, and percentage of myeloblasts. Patients with an isolated interstitial deletion of chromosome 5q31 represent a distinct subset who may derive particular benefit from immunomodulatory drugs. Goals of therapy for early MDS focus on hematologic improvement and maximizing quality of life. Thalidomide, the prototype of the immunomodulatory drugs, yields major erythroid responses in some patients with early MDS, but dose-limiting neurologic toxicities limit its potential clinical benefit. Lenalidomide, a more potent and non-neurotoxic derivative, has shown promising results in early MDS, yielding hematologic improvement in almost half of patients and transfusion independence with cytogenetic remissions in approximately two thirds of patients harboring the chromosome 5q31 deletion.

Introduction
The myelodysplastic syndromes (MDS) are remarkably heterogeneous stem cell malignancies that can be segregated into up to eight morphologic subtypes, depending on the pathologic classification system applied [1,2]. Attention to cytogenetic features, clinical parameters (including the number and types of peripheral blood cytopenias), the degree of bone marrow cell maturity (ie, the percentage of myeloblasts), and to morphologic characteristics is crucial in determining prognosis, as demonstrated with the International Prognostic Scoring System (IPSS) [3•]. The World Health Organization (WHO) classification system, for the first time, defined an MDS subtype based purely on cytogenetic findings—namely, an isolated interstitial deletion involving chromosome 5q31. Clinically, patients with this disorder are more often female (with a 7:3 ratio of female to male), have a normal or increased platelet count with dysplastic megakaryocytes, and have a disease that runs an indolent course with transfusion-dependent anemia [4]. This decision proved to be prescient, as a therapy has emerged that shows particular efficacy in this subtype of MDS.

In broad strokes, many divide MDS into “early” or indolent disease, in which proapoptotic forces predominate (frequently defined as “Low” or “Int-1” under the IPSS), and “late” or aggressive disease, in which proliferative factors prevail (frequently defined as “Int-2” or “High” by the IPSS). In early MDS, hematopoietic precursors have an impaired survival, in part because of the presence of inhibitory or inflammatory cytokines and enhanced angiogenesis [5–7]. In particular, vascular endothelial growth factor A (VEGF-A) not only promotes medullary neovascularity but also stimulates myeloblast clonal expansion and ineffective hematopoesis [6].

Therapeutic approaches capitalize on these distinctions. Thus, drugs that have shown more efficacy in advanced MDS are prodifferentiating, promote the transcription of tumor suppressor genes, or are directly cytotoxic. Agents targeting early MDS stimulate the remaining effective hematopoiesis, abrogate the effects of negative regulatory cytokines, or both. Recognizing this, an International Working Group (IWG) created universal measures of response to therapy in MDS [8••,9]. Implicit in the recommendations of this group are the differing therapeutic goals depending on MDS subtype. For patients with advanced MDS, the goals should be similar to those for patients with acute myeloid leukemia (AML): improving overall survival, attaining a complete remission, and, specific to MDS, preventing transformation to AML. For patients with early MDS, akin to chronic leukemias, goals center on minimizing transfusions and maximizing quality of life. One important aspect of the IWG criteria is the requirement that responses be maintained continuously for a minimum of 2 months. Unfortunately, once early MDS patients require two or
more red blood cell transfusions each month, growth factor therapy (including recombinant erythropoietin alone or in combination with colony-stimulating factors) often is ineffective [10,11•]. It is at this point in the disease course that tumor burden (eg, the number of myeloblasts or the cytokine effects from those dysplastic cells) overcomes the ability of intrinsic or extrinsic hematopoietic cell stimulatory factors to promote erythrocyte production, and chemotherapy should be considered.

**Thalidomide**

**Mechanism of action**

Thalidomide, an immunomodulatory drug, counters the proapoptotic forces in MDS through cytokine inhibition, immune modulatory effects, modulation of cell adhesion to bone marrow stromal cells, cytotoxic effects, and antiangiogenesis mechanisms of action, particularly through altering transforming growth factor (TGF) β and VEGF activity [12–15]. It is the first agent of this class of small molecule inhibitors of angiogenic cytokines to be investigated in MDS.

**Clinical studies in MDS**

Four phase II studies have evaluated thalidomide as single-agent therapy in MDS. In the largest, 83 patients with early and advanced MDS were evaluated, with the thalidomide dose escalated up to 400 mg per day in tolerant subjects [16••]. Of these patients, 58 had early MDS and 25 had advanced MDS. Hematologic improvement (defined as red blood cell transfusion independence or a greater than 50% decrease in transfusion burden) occurred in 15 patients (18%), 14 of whom had early MDS, including 10 previously transfusion-dependent patients who became transfusion-independent. Using IWG criteria, 11 patients had a major hematologic response and four patients had a minor hematologic response. In another study of 25 transfusion-dependent patients with MDS, five patients (20%) reached transfusion independence after treatment with thalidomide [17]. One other study of 34 patients with MDS showed varied hematologic lineage improvement in 19 (56%) after treatment with thalidomide [18]. A multicenter, phase II study, presented as an abstract and conducted by the North Central Cancer Treatment Group [19], reported a response in seven (10%) of 73 patients. This study was compromised by high early subject attrition (approximately two thirds of patients within 12 weeks) because of toxicity in the setting of aggressive dose escalation (from 200 to 1000 mg daily). In fact, toxicity-related discontinuations of thalidomide ranged from 12% to 40% across all of these studies, with the most common causes being fatigue, constipation, shortness of breath, and peripheral neuropathy that may not be reversible. The risk for development of these side effects is dose- and time-dependent and therefore limits long-term treatment and the ability to attain therapeutic dose levels—a discouraging reality, as patients who can tolerate the drug achieve hematologic response rates that approach 30%. Moreover, hematologic response to thalidomide is often delayed, with a median time to response of 16 weeks in the Rush Cancer Center trial [16••].

**Lenalidomide**

**Mechanism of action**

Lenalidomide (CC-5013, Revlimid, Celgene, Summit, NJ), an immunomodulatory drug, is a novel 4-amino-glutarimide analogue of thalidomide (Fig. 1). It has a similar mechanism of action to thalidomide and, when compared to thalidomide using in vitro studies measuring cytokine production and effects on multiple myeloma cell proliferation, it was found to be 50 to 2000 times more potent [12–15]. Other in vitro studies demonstrate the ability of lenalidomide to inhibit cellular response to activated VEGF receptors, inhibit VEGF-induced clonogenic response and VEGF expression in KG1 AML cell lines, and block VEGF-induced cell cycle recruitment and adhesion of KG1 AML cells [20]. Lenalidomide may also have effects on modulation of integrin affinity and promotion of progenitor responsiveness to erythropoietin.

**Clinical studies in MDS**

The studies of the efficacy of thalidomide in MDS patients provided the necessary rationale for testing lenalidomide in a similar patient population, particularly given the lack of toxicities that proved dose-limiting in the thalidomide studies. Only three clinical trials have investigated the use of lenalidomide in MDS patients, and only one has been published, though preliminary results of the two multicenter studies were presented in part in the education session on MDS at the American Society of Hematology 2004 annual meeting.