Myelodysplastic syndromes (MDS) are a group of heterogeneous hematopoietic stem cell disorders characterized by peripheral blood cytopenias and a risk of transformation to acute myeloid leukaemia (AML).1 With a median age at diagnosis around 70 years, MDS typically affects the elderly.3,4 Hence, there is much morbidity and mortality associated with this patient population, as patients frequently suffer from complications due to cytopenias as well as other comorbidities. The two systems used for classifying MDS are the French American and British (FAB) criteria and the more recently revised World Health Organization (WHO) classification system. A third system, the International Prognostic Scoring System (IPSS), can predict survival based on percentage of bone marrow blasts, karyotype and number of peripheral blood cytopenias5 and is the most widely used prognostic tool for assisting with treatment decisions.

For many years, supportive care with blood products (red blood cell [RBC] and platelet transfusions), hematopoietic growth factors and antibiotics remained the only treatment modality for MDS patients, until the development of three novel agents that may alter the natural history of this disease. Within the past decade, the US Food and Drug Administration (FDA) has approved an immunomodulatory agent, lenalidomide (Revlimid™, Celgene) and two hypomethylating agents, decitabine (Dacogen™, Eisai, Inc.) and azacitidine (Vidaza™, Celgene) for the treatment of patients with MDS. In simple practice, therapy is tailored to IPSS score with an emphasis on supportive care therapies or lenalidomide for lower-risk patients (IPSS low or intermediate [int]-1) and more intensive therapies such as conventional chemotherapy, allogeneic hematopoietic stem cell transplant (HST) and clinical trials, as well as hypomethylating agents, for patients with higher-risk disease (IPSS int-2 or high) or lower-risk patients with progressive disease.5,6

**Treatment of Lower-risk Myelodysplastic Syndromes**

**Supportive Care**

Initial clinical management of lower-risk MDS patients with symptomatic anemia includes the use of erythropoiesis stimulating agents (ESAs), such as epoetin alpha (Epopogen™, Amgen; Procrit™, Ortho Biotech) or darbepoetin alpha (Aranesp™, Amgen). ESAs have been shown to reduce RBC transfusion needs in MDS patients and when given with granulocyte colony-stimulating factor (G-CSF), ESAs have been shown to confer a survival advantage.7 The likelihood of response to ESAs has been correlated with RBC transfusion needs and serum erythropoietin (EPO) levels. Patients with low transfusion requirements (<two units packed red blood cells [pRBC] per month) and serum EPO levels >500 mU/ml are predicted to have a good response to ESAs and G-CSF, whereas patients with higher transfusion needs (>two units pRBC per month) and serum EPO levels ≤500 mU/ml are least likely to respond to ESAs.7,8 Demonstrated in a recent prospective, randomised study by the Eastern Cooperative Oncology Group (ECOG), patients with low-risk MDS and low serum EPO levels experienced higher erythroid response rates when given ESAs with or without G-CSF compared with patients with high-risk disease.7

**Immunosuppressive Therapy**

A subset of MDS patients with bone marrow failure responds to immunosuppressive therapy (IST), which suggests that an immune-
mediated pathogenesis is responsible for the cytopenias. In patients with
hypocellular bone marrow, IST with antithymocyte globulin (ATG),
cyclosporine or both can be utilised. In patients with MDS, ATG alone has
been shown to decrease RBC transfusion requirements as well as
improve neutropenia and thrombocytopenia.12,13 Likewise, long-term
outcomes in low-risk MDS patients have shown higher response rates
with ATG and cyclosporine (54 %) than ATG alone (29 %) (p=0.004).3
Factors that have been shown to favour response to ATG include age,9,10
human leukocyte antigen (HLA)-DR15 positivity9,10 and shorter duration of
RBC transfusion requirements.5,6 In general, patients will respond to IST
within three to four months and will remain clinically stable for years, but
many eventually relapse with return of cytopenias. Recently, a Phase II pilot
study demonstrated alemtuzumab, an anti-CD52 monoclonal antibody,
duces durable responses in patients with intermediate-risk MDS who fit criteria to respond to IST. Ninety-seven per cent of int-1-risk
patients and 57 % of int-2 patients responded to alemtuzumab by three
months, which was superior to response rates reported with ATG alone.8
Furthermore, at 12 months follow-up, 56 % of responding patients had
normal blood counts and 78 % of patients were transfusion independent.11

Immunomodulating Therapy—Lenalidomide
Lenalidomide was FDA approved in 2005 for the treatment of patients with
transfusion-dependent anaemia due to low- and int-1-risk MDS associated
with deletion 5q karyotype [del(5q)]. The approval of lenalidomide was
based on two Phase II studies demonstrating a high frequency of erythroid
responses in patients with an isolated del(5q) or del(5q) with other
abnormalities.12,13 The majority of patients in these studies were IPSS low-
or int-1-risk patients with transfusion-dependent anaemia. The majority of
patients achieved a hematologic response (reduced transfusion needs) and
to became transfusion independent. Not of note, responses occurred despite
karyotype complexity and patients with thrombocytopenia at baseline were
less likely to respond to lenalidomide compared with patients with platelets
>100,000/ml at baseline. Furthermore, a majority of patients had
cytogenetic improvement and 45 % had a complete cytogenetic response.
Hence, these responses illustrate the effect of lenalidomide on the biology
of the disease by reversing the cytogenetic abnormalities associated with
the 5q31 deletion.13 Following these studies, Raza et al. evaluated the safety
and efficacy of lenalidomide in 214 patients with transfusion-dependent
anaemia due to lower-risk MDS without del(5q). Hematologic responses were
lower than those observed in patients with del(5q), but the rate of
transfusion independence was 26 % and the median duration of transfusion
independence was 41 weeks.15 Lenalidomide demonstrated a potential
benefit for low-risk patients without del(5q) who remain transfusion
dependent after supportive care measures or for patients who are not
candidates for ESAs or more intensive therapy. Although lenalidomide is
generally well tolerated, it induces significant cytopenias resulting in dose
reduction or interruption in a majority of patients.

Treatment of Higher-risk Myelodysplastic
Syndromes

Hypomethylating Agents

Azacitidine and Decitabine
Azacitidine and decitabine are both hypomethylating agents that
irreversibly inhibit DNA methyltransferase, resulting in progressive loss
of methylation and reactivation of tumour suppressor genes. Azacitidine
was the first DNA methyltransferase inhibitor approved by the FDA in
2004, for the treatment of all FAB subtypes of MDS. This approval was
based on the results of three Cancer and leukemia group B (CALGB)
studies that evaluated the efficacy and safety of azacitidine 75 mg/m²
intravenous (IV) or subcutaneous (SQ) x seven days every 28 days in MDS patients. A pooled analysis of the CALGB trials (8421, 8921
and 9221) reported overall response rates (ORR) between 40 and 47 %
(complete remission (CR) 10–17 %, partial remission (PR) 1 %,
hematological improvement (HI) 23–36 %) for azacitidine and 17 % (HI
only) for best supportive care (BSC) by International Working Group (IWG)
2000 criteria.15,16

Subsequently, the AZA-001 trial established an improved overall
survival in patients with higher-risk MDS. In this Phase III trial, 358
patients with IPSS int-2- or high-risk MDS were randomized to receive
azacitidine (75 mg/m² SQ daily x seven days, every 28 days) or
conventional care (BSC, low-dose cytarabine, or intensive chemotherapy).
The overall survival was significantly longer with azacitidine compared with conventional care (24.5 versus 15 months;
hazard ratio (HR): 0.58; 95 % confidence interval (CI): 0.43–0.77;
p=0.0001) and was present regardless of MDS subtype and IPSS
subgroup. The median time to AML transformation was improved with azacitidine compared with conventional care (17.8 versus 11.5
months; HR: 0.5; 95 % CI: 0.35–0.7; p<0.0001). By IWG criteria,15
azacitidine-treated patients demonstrated higher response rates.17

In 2006, decitabine was also approved for the treatment of all FAB
subtypes of MDS. This approval was based on the results of a Phase III
multicenter trial that randomized 170 MDS patients to treatment with
decitabine at 15 mg/m² IV over three hours every eight hours for three
consecutive days every six weeks (135 mg/m²/course) or to BSC.16 More
than half of the patients had higher-risk MDS. By IWG criteria,16 the ORR
for the decitabine arm was 30 % (CR 9 %, PR 8 %, HI 13 %) compared with
7 % (CR 0 %, PR 0 %, HI 7 %) with BSC (p<0.001). Although there was a
trend for improved time to AML progression or death in patients treated
with decitabine (12.1 versus 7.6 months, p=0.16), it was only significant
when analyzing the subgroup with IPSS int-2- or high-risk disease (12.3
versus 7.3 months, p=0.03). There was no difference in overall survival
between the two groups.16 The European Organization for Research and
Treatment of Cancer (EORTC) and the German MDS Study Group
conducted a similar Phase III study, using the same dose of decitabine.16
This trial randomized 233 elderly patients with higher-risk MDS to either
decitabine or BSC and confirmed similar response rates with an ORR,
by IWG criteria,15 of 34 % (CR 13 %, PR 6 %, HI 15 %) with decitabine
compared with 2 % (HI only) with BSC. Despite an improvement in
progression-free survival with decitabine, there was no difference
in overall survival or time to AML between the two groups. A median
of four cycles were given; however, 40 % of patients received no more
than two cycles.18

Interested in optimizing the hypomethylation properties of decitabine, a
lower dose of decitabine (100 mg/m²/course) was subsequently evaluated
at the MD Anderson Cancer Center (MDACC) in a Phase II trial that
compared three different schedules of decitabine: 10 mg/m² IV over one
hour daily for 10 days, 20 mg/m² IV over one hour daily for five days or
20 mg/m² SQ daily for five days every four weeks.20 The ORR by modified
IWG criteria15 was 73 % (CR 34 %, PR 1 %, marrow CR [mCR] 24 % and HI

Hematological Malignancies
Patients require several courses of azacitidine and decitabine (three to six cycles) before demonstrating a response, so drug- and disease-induced myelosuppression can be common during this time period. Therefore, treatment should continue with both agents for a minimum of three to four cycles before declaring therapy a failure. Although azacitidine is an outpatient regimen, it is complicated by a seven-consecutive-day regimen, necessitating weekend administration. More convenient regimens (i.e. five-day, five days followed by two additional weekdays) have been explored in predominately lower-risk patients and response rates appear similar among the three regimens.24,25 However, it is not certain that these regimens will lead to a survival advantage in higher-risk MDS patients.

**Stem Cell Transplant**

The only potential curative option for MDS is allogeneic hematopoietic stem cell transplant (HSCT), but it is restricted to patients with a donor and those free from co-morbidities that may preclude them from this option.

For patients older than 55 years, the mortality rate is approximately 38%. For patients who are eligible for HSCT, the timing of transplantation is important. Published data identifying the optimal timing of HSCT is scant. However, a retrospective analysis of patients younger than 60 years of age who received a myeloablative conditioning regimen from a sibling donor transplant suggests that survival is better for low- and int-1-risk patients receiving a transplant at the time of disease progression rather than at diagnosis. Outcomes for int-2- and high-risk patients are better when transplantation is performed as early as possible.26 Therefore, donor screening for younger patients should begin as soon as possible regardless of the IPSS score at diagnosis. This sheds some light on the timing for younger patients. For elderly patients, reduced-intensity transplants may be an option.

**Conclusion**

Patients with MDS are predominately elderly and have multiple comorbidities that preclude them from curative therapies. For many years, supportive care measures remained the only treatment modality for MDS patients, until the development of three novel agents that may alter the biology of this disease. The recent development of three FDA-approved agents, lenalidomide, azacitidine and decitabine, has dramatically changed the MDS landscape. Lenalidomide is remarkably effective in lower-risk patients, producing complete or nearly complete transfusion independence in the majority of del(5q) and some non-del(5q) patients. The hypomethylating agents azacitidine and decitabine are effective in the setting of higher-risk MDS patients, producing responses in nearly half of treated patients. Compared with conventional care regimens, azacitidine has significantly improved the median survival of higher-risk patients. Despite these therapeutic advances, the responses in higher-risk patients are not durable, making the search for other novel agents necessary.