How I Treat

How we treat lower-risk myelodysplastic syndromes

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How we treat lower-risk myelodysplastic syndromes (MDSs) are defined as having low or intermediate-1 risk by the International Prognostic Scoring System and are characterized mainly by anemia in most cases. Supportive care—primarily red blood cell transfusions—remains an important component of their treatment, but exposes patients to insufficient correction of anemia, alloimmunization, and organ iron overload (for which the role of iron chelation remains debated). Treatment aimed at preventing anemia recurrence should therefore be used whenever possible. Erythropoiesis stimulating agents remain the first-line treatment of anemia in most lower-risk MDS without del(5q), whereas anemia of low-risk MDS with del 5q responds to lenalidomide in two-thirds of the cases, but this drug should be used cautiously because profound cytopenias may occur initially. Treatment after failure of those first-line therapies are disappointing overall, with many patients eventually requiring long-term transfusions, but encouraging results have been reported with hypomethylating agents and lenalidomide. Selected patients respond to antithymocyte globulins, and thombopoietin receptor agonists are under investigation in lower-risk MDS with thrombocytopenia. Some patients, while remaining at a “lower risk” MDS level, have severe cytopenias and/or poor prognostic factors, found using newer prognostic parameters, or resistance to treatment, making them urgent candidates for more intensive approaches, including allogeneic stem cell transplantation. (Blood. 2013;121(21):4280-4286)

Myelodysplastic syndromes (MDSs) are clonal stem cell disorders characterized by ineffective hematopoiesis leading to blood cytopenias, and by a high incidence of progression to acute myeloid leukemia (AML). The pathophysiology of MDS is a multistep process involving genetic changes detectable by conventional cytogenetic techniques or smaller anomalies detectable only by more sophisticated methods like single nucleotide polymorphism array technology or sequencing techniques. Somatic mutations, now detected in most MDS cases, can involve genes encoding signaling molecules (NRAS, KRAS, CBL, JAK2, FLT3), epigenetic regulators (TET2, ASXL1, EZH2, UTX, IDH1, IDH2, DNMT3A, SETBP1), splicing factors (SF3BI, SRSF2, ZRSF2, U2AF1), and transcription regulators (RUNXI, NPM1 and TP53). Widespread gene hypermethylation, on the other hand, is a major finding during progression of MDS.

Main prognostic factors in MDS include the number and importance of cytopenias, marrow blasts percentage, and marrow cytogenetic abnormalities combined in a “classic” International Prognostic Scoring System (IPSS) (that was very recently revised [IPSS-R]) that distinguishes between various subgroups with significantly different risk of progression to AML and survival. Other prognostic factors include the presence of grade ≥2 marrow fibrosis, certain somatic gene mutations, and possibly some flow cytometry parameters, but the last 2 tests are currently not routinely performed in most laboratories.

Although the division is schematic, it is customary since publication of the classic IPSS to separate MDS into “higher risk” (corresponding to IPSS high or intermediate-2) and “lower risk” (corresponding to IPSS low or intermediate-1). Higher-risk MDS carry a major risk of progression to AML and short survival, and treatment in those patients should aim, whenever possible, to modify the natural disease course. Treatments used in higher-risk MDSs therefore include allogeneic stem cell transplantation (SCT); the hypomethylating agents (HMAs), azacitidine (AZA), and decitabine; and, although currently less often, chemotherapy (mainly intensive anthracycline-AraC combinations). In lower-risk MDS, the risk of AML progression is less and survival is longer, with approximately one-half of those elderly patients dying from a cause other than the consequences of MDS or AML. In those patients, the main priority is generally the treatment of cytopenias, mainly of anemia (usually the predominant cytopenia), and the improvement in quality of life. Still, some of those patients may be identified, either rapidly by their revised IPSS score or by other biological characteristics, or subsequently by their resistance to first-line treatment as having a poorer prognosis, and they may benefit from treatments generally applied to higher-risk MDS.

How do we treat cytopenias in lower-risk MDS?

Anemia, the predominant cytopenia in most cases of lower-risk MDS, is in general the primary focus. It often requires repeated red blood cell (RBC) transfusions, leading to potential iron overload.

Treatment of anemia

RBC transfusions or drugs? Chronic RBC transfusions could be considered an only treatment of anemia of lower-risk MDS, because very few drugs are approved in this situation and none has clearly demonstrated that it could improve survival. However, chronic RBC transfusion are associated not so much with risks of viral infection or of alloimmunization, which are now very low, but with chronic anemia (ie, average hemoglobin levels <10 g/dl), leading to increased morbidity, especially as a result of cardiac failure, falls, fatigue, and lower quality of life. Transfusions are also time-consuming for the patient, induce their “dependence” toward the


4280 BLOOD, 23 MAY 2013 • VOLUME 121, NUMBER 21
medical system, and require the use of hospital beds, and their cost (including patient transportation, serum testing, iron chelation, etc.) is important, although generally lower than that of erythropoiesis stimulating agents (ESAs). Although this remains disputed (discussed later), iron overload as a result of RBC transfusions may also be deleterious to various organs.\textsuperscript{33,31} Finally, we and others also recently found that in lower-risk MDS with anemia, receiving ESAs had no impact on progression to AML but was an independent favorable prognostic factor for survival, although it was unclear whether this was because of ESA treatment itself or to maintaining hemoglobin levels >10 g/L or avoiding iron overload.\textsuperscript{34-37}

What is our first-line treatment of anemia in lower-risk MDS? Patients without del(5q): ESAs. ESAs (ie, recombinant erythropoietin (EPO) or darbepoetin [DAR]), remain the first choice of treatment of anemia in most lower-risk MDS without del(5q). Major favorable prognostic factors for response to ESAs are low or no RBC transfusion requirement (<2 U per month) and baseline serum EPO level <500 U/L.\textsuperscript{38} Most lower-risk MDS are now considered for anemia treatment when no or limited RBC transfusions are required, and in our experience their EPO level was <200 U/L in 62% of the cases.\textsuperscript{34} Weekly doses of 40 000 units of EPO-α (Procrit or Eprex), 30 000 units of EPO-β (Recormon), or 150 to 300 μg of DAR (Aranesp) yield approximately 60% of erythroid responses, according to IWG 2006 response criteria.\textsuperscript{39} when the baseline EPO level is low and transfusion requirement is limited or absent,\textsuperscript{34,36,40} and response rates appear to be somewhat higher using 60 000 vs 30 000 U per week of EPO, and 300 μg vs 150 μg per week of DAR. The efficacy of ESAs can be further improved by the addition of granulocyte colony-stimulating factor (G-CSF),\textsuperscript{38,42} although to a lesser extent when high doses of ESAs (60 000 U/week of EPO or 300 μg/week of DAR) are used. Contrary to previous findings, we did not find in 2 large patient series that RARS or RCMD (17/RS) responded less favorably to an ESA alone than to RA.\textsuperscript{34,43} Finally, there are no data showing that one ESA could be superior to another.

Most responses to ESA occur within 8 weeks of treatment, although some patients respond after only 12 weeks. During initial treatment, close monitoring of hemoglobin level is required to avoid increases to >12 g/dL, which is associated with a potential risk of systemic hypertension and thrombosis when ESAs are used to treat renal failure (although they have not been documented in MDS). Supplemental oral or intravenous iron is advocated mainly in case of relapse of anemia after initial response to ESAs, because prolonged ESA may lead to iron deficiency.\textsuperscript{44}

Median duration of response to ESA is approximately 2 years, and responses are longer in patients with major response according to IWG 2000 criteria,\textsuperscript{39} IPSS low or intermediate-1, marrow blasts <5%, and no multilineage dysplasia.\textsuperscript{34,35,45} Interestingly, approximately 70% of the relapses of anemia after initial response to ESAs are not associated with progression to higher-risk MDS but simply to loss of sensitivity of erythroid progenitors to ESAs,\textsuperscript{34} and second-line treatments in those patients may be different from those required in patients showing concomitant progression to higher-risk MDS.

Lower-risk MDS with del 5q: lenalidomide. Anemia of lower-risk MDS with del 5q compared with that of other lower-risk MDS, showed lower response rates to ESA (39% vs 52% in our experience) and significantly shorter responses to ESA (median 1 year vs 2 years).\textsuperscript{46} However, it dramatically responds to lenalidomide (LEN), approved by Food and Drug Administration in this indication if anemia is transfusion-dependent (TD), based on 2 large studies (MDS 003 and 004 trials).\textsuperscript{37,48} In those trials, LEN (5-10 mg/day) yielded RBC transfusion-independence (RBC-TI) in 55% to 65% of the subjects, with a median duration of RBC-TI of 2 to 2.5 years.\textsuperscript{47,48} Cytogenetic response was achieved in 50% to 73% of subjects (including 30%-45% complete responses). Combining results of those 2 studies showed higher RBC-TI and cytogenetic responses with a daily dose of 10 mg (compared with 5 mg), less RBC-TI in patients with cytogenetic abnormalities in addition to del 5q, and high RBC-TD.\textsuperscript{49} TP53 gene mutations, found in about 20% of lower-risk MDS with del 5q, seem to confer resistance to LEN and a higher risk of AML progression,\textsuperscript{50} and their presence may require more aggressive treatment.

Grade 3 or 4 neutropenia and thrombocytopenia, seen in approximately 60% of the patients during the first weeks of treatment, constitute the most common adverse events of LEN.\textsuperscript{47,48} Close monitoring of blood counts is therefore required during this period, as well as drug discontinuation made if absolute neutrophil count decreases to <0.5G/L or platelets <25 G/L, and the drug restarted at a half dose upon correction of cytopenias.\textsuperscript{51} Addition of G-CSF can however be recommended if ANC <1 G/L, to avoid neutropenia and further dose reductions of LEN, because higher LEN doses may be associated with better erythroid and cytogenetic responses, as mentioned before.\textsuperscript{51} The thrombopoietin (TPO) receptor agonist romiplostim may reduce thrombocytopenia in that context, but it is not available for routine practice.\textsuperscript{52}

Other side effects of LEN in low-risk MDS with del 5q include deep venous thrombosis (DVT) and/or pulmonary embolism. Although DVT was observed in 8 of the 95 patients treated in the French patient–named program,\textsuperscript{53} it was reported in only 0.53% of more than 7500 MDS treated with LEN in a US postmarketing experience, but the incidence was higher in patients with concurrent use of EPO.\textsuperscript{54} Prophylactic measures for DVT in MDS treated with LEN are not codified, except in patients with a history of DVT, where prophylactic anticoagulation is probably justified.\textsuperscript{51}

Rash is frequent, although generally transient, with LEN in MDS, whereas diarrhea can be long lasting, with limited efficacy of symptomatic treatment.\textsuperscript{57,55}

In responders, the optimal duration of LEN treatment is unknown. Because stem cell with del(5q) persist in responders,\textsuperscript{56} prolonged treatment may be required to avoid rapid relapse. On the other hand, drug discontinuation in patients who have achieved complete cytogenetic response may be associated with prolonged responses.\textsuperscript{57}

Although Food and Drug Administration approved LEN in lower-risk MDS with del 5q, the European Medicines Agency raised concern over a potential risk of LEN to trigger AML progression in some lower-risk MDS with del 5q and requested additional analyses. In the absence of prospective randomized trials, 3 retrospective analyses comparing the long-term outcome of lower-risk MDS with del 5q treated with and without LEN found no excess risk of AML with lenalidomide.\textsuperscript{38,55} Until a new European Medicines Agency examination, therefore, EU investigators should use LEN as a second-line treatment, after ESA failure, and preferably in a clinical trial. Because LEN is currently approved only in the case of RBC-TD, patients with non-TD anemia may also be candidates for ESA. Furthermore, LEN is currently indicated only in cases of RBC TD anemia, and patients with lower-risk MDS with del 5q with non–TD anemia are also candidates for first-line treatment with ESAs.

What are our second-line treatments for anemia of lower-risk MDS? Patients without del 5q. Treatment after ESA failure (primary resistance or relapse after a response) in patients who remain with IPSS low or intermediate-1 score for MDS remains disappointing overall. Most patients eventually require long-term RBC transfusions. In our experience, early ESA failure (no response
to ESA or relapse within 6 months) is a marker of disease severity associated with frequent subsequent AML progression and a median survival of only 3 years.60 In such patients, second-line treatments with a potential impact on disease course may need to be considered. The second-line treatments we currently use include antithymocyte globulin (ATG), HMAs, and LEN.

ATG: ATG, with or without cyclosporine, can yield an erythroid response (associated with response on other cytopenias, especially thrombocytopenia), in 25% to 40% of patients treated.61-66 Response rates, however, depend largely on the population treated. ATG results are better in relatively young (<65 years) low-risk MDS patients with a RBC transfusion history of <2 years, with normal karyotype (or possibly trisomy 8), with no excess blasts, HLA DR15 genotype, and possibly in patients with thrombocytopenia in addition to anemia, a small PNH clone, or marrow hypocellularity.61 In the French registry of MDS, the patients represented only 6.5% of the low-risk MDS, suggesting that good ATG candidates may be relatively rare in MDS.67 ATG may also be considered in patients in whom thrombocytopenia is the predominant cytopenia.

More recently, alemtuzumab treatment in 32 lower-risk MDS patients who had favorable criteria for ATG response, yielded a 77% response rate, sustained improvement in blood counts, and cytogenetic remissions.68 However, the drug is not widely available in this indication. In addition, this patient series was highly selected, because it included patients with good prognostic factors of response to immunosuppression.

Hypomethylating agents: HMAs have been reported to yield RBC-TI in 30% to 40% of patients and may also be effective for other cytopenias in lower-risk MDS. They are approved in this situation in several countries, including the United States. In a phase II trial randomizing AZA and AZA + EPO in RBC TD lower-risk MDS clearly identified as resistant to ESA; however, we observed only 17% RBC-TI, without difference between the 2 treatment arms, possibly suggesting lower efficacy in patients who are clearly ESA resistant.71

We use HMAs as second-line treatment particularly in patients with thrombocytopenia in addition to anemia (or isolated thrombocytopenia). Even though they have not demonstrated a survival advantage in low-risk MDS, we also use them in patients with early ESA failure (no response or relapse within 6 months of response), whose progression rate and survival is rather unfavorable.60 Lenalidomide: Lenalidomide yields RBC-TI in 25% to 30% of lower-risk MDS without del 5q resistant to ESA.72-75 Because it induces neutropenia and thrombocytopenia (although to a lesser extent than in patients with del 5q), it is difficult to use when those cytopenias are present in addition to anemia. Furthermore, it is unclear whether LEN, in addition to improving anemia, has any effect on disease progression and survival in those patients. Therefore, LEN, in non-del 5q patients, appears justified only in clinical trials. Preliminary results suggest that the combination of LEN and ESA may yield high RBC-TI rates in patients resistant to an ESA alone, and we are currently trying to confirm those results in a prospective, randomized trial.74

Patients with del 5q: Results of the MDS 003 and MDS 004 trials47,48 (described before) also suggest that resistance to LEN in lower-risk MDS with del 5q is associated with poor prognosis, even if no immediate progression to high-risk MDS is observed. Patients with TP53 gene mutation may have a particularly poor outcome.70 Although no prospective data exist, those patients should probably be candidates to approaches having demonstrated a survival benefit in MDS, including HMAs, and whenever possible allogeneic SCT. Our recent experience with AZA after LEN treatment failure showed a 50% response rate and a median overall survival of 32 months in responding patients.75

Long term RBC transfusions and iron chelation therapy.

In many patients with lower-risk MDS, anemia will eventually become resistant to all available drug treatments, even in the absence of evolution to higher-risk MDS, and will require repeated RBC cell transfusions.60 For those patients, it is recommended to administer transfusions at sufficiently high hemoglobin thresholds (ie, at least 8 g/dL and 9 or 10 g/dL, in cases of comorbidities worsened by anemia [eg, coronary artery disease, heart failure] or in cases of poor functional tolerance). In addition, a sufficient number of RBC concentrates should be transfused each time, over 2 or 3 days if needed, to increase the hemoglobin level to >10 g/dL and thereby limit the effects of chronic anemia.

A large debate exists about the deleterious effect of iron overload in MDS patients and whether iron chelation may be useful in patients with iron overload. In particular, although heart iron overload is a well-documented cause of heart failure in children with thalassemia,76,77 its incidence and clinical consequences are uncertain in RBC-transfused MDS patients, especially as many of them already have other causes of cardiac morbidity. Some authors may therefore consider that in those patients, iron overload is just one cause of cardiac failure,78 whereas others may consider that this additional cause may precipitate a sometimes unstable cardiac situation.79,80 Discrepancies are also probably related to the variable median number of RBC units transfused in different published series. Indeed, significant iron overload appears to occur later in the heart than in other organs, especially the liver. However, heart magnetic resonance imaging studies show that heart iron overload (reflected by a decrease in heart T2* imaging) is frequent in patients having received at least 70 to 80 RBC concentrates or more, a frequent situation in low-risk MDS, and that a heart T2* value <20 ms is associated with decreased left ventricular ejection fraction and a risk of heart failure.81

Thus, very heavily RBC-transfused MDS patients develop major iron overload, especially in the heart and liver, which may reduce survival owing to cardiac failure or liver cirrhosis. It has been suggested in 3 retrospective studies that adequate chelation in highly transfused patients may improve their survival.82-84 Prospective, randomized studies are underway to confirm those results, but they are difficult to conduct because 2 chelating agents (deferoxamine and deferasirox) are approved for this indication in MDS.

In the absence of prospective studies, published recommendations for iron chelation therapy only result from expert opinions.85,86 We generally advocate starting chelation in patients with relatively favorable prognosis (ie, low or intermediate–1-risk MDS) who have received at least 50 to 60 RBC concentrates, or if serum ferritin increases >2500 U/L or if cardiac T2* findings are significantly reduced. Future candidates to allogeneic SCT are an exception. Indeed, although the underlying mechanisms are unclear, there is a consensus that even relatively moderate iron overload before allogeneic SCT is associated with increased transplant-related mortality.87-90 In addition, intensive chelation treatment before transplant may improve survival in those patients, although this was observed in a retrospective study only.91 Thus, in MDS patients who may eventually be candidates for allogeneic SCT, we start iron chelation after around 20 RBC concentrates or above a serum ferritin level of 1000 UI. The same thresholds have been advocated in low-risk MDS as a whole in some recommendations.85,86 put, as stated before, they not based on prospective studies.

Iron chelation is now made easier by the availability of oral iron chelators (especially deferasirox), in addition to the classical parenteral
we ask our neutropenic patients to take amoxicilline-clavulanic acid. However, deferasirox is frequently associated with gastrointestinal side effects and cannot be used in patients with renal failure.92 Deferiprone, another oral iron chelator, is currently not approved for MDS in most countries and can cause neutropenia in a small percentage of patients, a side effect that is problematic in MDS.93

**Treatment of neutropenia and thrombocytopenia**

In lower-risk MDS, neutropenia and thrombocytopenia are less frequent than anemia and are infrequently isolated or profound. Neutropenia. WBCs are <1.5 mm\(^3\) in only 7% of lower-risk MDS,94 and neutropenia is rarely associated with life-threatening infection if no drugs that worsen neutropenia are used. G-CSF and granulocyte macrophage-CSF can improve neutropenia in 60% to 75% of those cases, but their prolonged use has not demonstrated an impact on survival, whereas a risk of stimulating progression to higher-risk MDS or AML has not been formally excluded. They may be used for transient periods, in patients who have severe sepsis, but this has never occurred in our clinical practice. Immediate use of broad-spectrum antibiotics should be recommended to neutropenic MDS patients in case of fever or other signs of infection. In the absence of a previous infection episode with resistant strains, we ask our neutropenic patients to take amoxicilline-clavulanic acid and ciproflaxacin immediately in case of fever and then contact their physicians.

Thrombocytopenia. Platelets <50,000/mm\(^3\) are seen in approximately 30% of low-risk MDS,94 and severe bleeding is relatively rare unless drugs interfering with hemostasis are used. We sometimes use high-dose androgens, which can improve thrombocytopenia in approximately one-third of thrombocytopenic lower-risk MDS, but the response is generally transient.95–96 Growth factors nonspecific of the platelet lineage, including interleukin (IL)3, IL6, and IL11, have been used with some success, but they also produce side effects.95,97,98

In exceptional cases, a peripheral mechanism of platelet destruction may predominate in MDS, as evidenced by platelet lifespan studies, with a possible success of splenectomy in our experience.99

Because TPO itself is immunogenic, leading to thrombocytopenia, TPO receptor agonists including romiplostim and eltrombopag have been designed to treat thrombocytopenias of different origins. Romiplostim at a high dose (500-1500 μg/week) yielded 55% platelet responses in a phase II trial in lower-risk MDS with thrombocytopenia.100 However, in approximately 15% of the patients, a transient rise in marrow blasts was seen but was reversible after drug discontinuation. In a randomized phase II study vs placebo in lower-risk MDS with thrombocytopenia, romiplostim reduced the incidence of severe bleeding and platelet transfusions, but there was a suspected increase in the risk of AML, and data are currently under review.101 Currently, TPO agonist receptors are unavailable for routine practice.

ATG and HMAs appear to elicit platelet response in 35% to 40% of the cases of lower-risk MDS, in addition to erythroid responses, and we sometimes use them in this context.52,66,102–104

### Identifying lower-risk MDS with poorer outcome

Although management of cytopenias, mainly anemia, is generally the major clinical objective in lower-risk MDS, some patients may have, at diagnosis or during evolution, features associated with a risk of progression to high-risk MDS/AML or life-threatening cytopenias that may justify treatment strategies aimed at modifying the disease course, especially with HMAs and, in some younger patients, even lead to the consideration of allogeneic SCT.

**Identifying lower-risk MDS patients with poorer outcome**

**At presentation.** The “classical” IPSS,22 defining lower-risk MDS as low and intermediate-1 risk IPSS, appears to be insufficient, especially because it does not incorporate marrow multilineage dysplasia80 or RBC transfusion dependence,80 associated with poorer prognosis, as well as severity of thrombocytopenia,23 and because some cytogenetic abnormalities like those involving 3q21-26 are considered an intermediate prognosis.

Some of those caveats are addressed by the World Health Organization classification–based Prognostic Scoring System,80 and more importantly by the revised IPSS,23 that appear to better discriminate prognosis in classical IPSS low and intermediate-1 MDS. For example, in IPSS low and intermediate-1 patients, 27% were shifted to higher-risk IPSS-R categories, mainly intermediate-2.

Presence of grade 2 or higher myelofibrosis in lower-risk MDS is also associated in some series with a higher risk of AML progression and poorer survival,24 although this parameter lacked prognostic significance in the IPSS-R cohort.23

A M. D. Anderson scoring system for IPSS low and intermediate-1 patients, based on specific thresholds for platelets, hemoglobin, age, marrow blasts, and cytogenetics, was also capable of better discriminating the prognosis of IPSS lower-risk MDS, whereas presence of somatic mutations, especially of EZH2 gene, added independent poor prognostic value to this score.106

**During follow-up.** Lower-risk MDS patients (according to IPSS) who remain at lower risk but have early resistance to ESAs (non-del 5q patients65 or resistance to LEN (del 5q patients),88 and who develop a cytogenetic abnormality or a life-threatening cytopenia (mainly thrombocytopenia) also have relatively poor survival.

**How we manage those patients**

Although prospective studies are lacking, we increasingly use HMAs (based on their known effect on survival in high-risk MDS) treatment in classic IPSS “lower-risk” patients.

We also consider allogeneic SCT in patients aged <60 to 65 years with a human leukocyte antigen (HLA)–identical donor and no contraindication to the procedure, in case of life-threatening thrombocytopenia; karyotype considered as unfavorable by IPSS-R (including 3q26 rearrangements); TP53, EZH2, or ASXL1 mutation; and in the absence of major response to HMAs (or subsequent relapse).

### Conclusion

Chronic anemia remains the most frequent clinical problem in lower-risk MDS, which alters quality of life in those elderly patients. ESAs generally constitute the first-line treatment of anemia except in patients with 5q deletion, in whom results of LEN are superior, but responses to both treatments are generally transient. Second-line treatments of anemia (including HMAs, LEN in the absence of 5q deletion, and ATG) are less satisfactory, yielding at best one-third of responses, so that many patients eventually require more effective strategies.
repeated RBC transfusions, a situation in which indications for iron overload prophylaxis are still somewhat disputed. In a majority of lower-risk MDS, thrombocytopenia is the predominating cytopenia, and TPO agonist receptors are currently being tested in this situation, whereas HMA or ATG may be useful. Some patients with lower-risk MDS according to IPSS may, at diagnosis or during evolution, have features associated with poorer prognosis, based on new prognostic scoring systems (eg, IPSS-R, M.D. Anderson score), presence of gene somatic mutations, or resistance to first-line treatment, that may consider them for more intensive treatment, including in some cases allogeneic SCT.

References


Authorship

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