# BHS 2013 recommendations for treatment of myelodysplastic syndromes

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**The guidelines on the current state-of-the-art in the diagnosis and treatment of myelodysplastic syndromes of the Belgian Hematological Society working group on myelodysplastic syndromes were published in 2013.[1] The key points of these guidelines are presented in two issues of the Belgian Journal of Hematology. In this paper we present the optimal treatment of patients with myelodysplastic syndromes within the current limitations of Belgian reimbursement modalities.**

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## Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of haematological disorders. Over the past few years several new drugs have emerged that have altered the management of patients suffering from MDS. However, due to reimbursement limitations, they are not available to Belgian patients who may possibly benefit from them. The choice of the optimal treatment relies on accurate diagnosis and assessment of comorbidities. It should therefore be emphasised that in addition to the time of diagnosis, also at disease progression or treatment failure, it is recommended to repeat at least a bone marrow aspirate (for enumeration of blast count) and cytogenetics.

## Hematopoietic growth factors

Treatment with erythropoiesis stimulating agents (ESAs) can improve haemoglobin levels and alleviate transfusion need in low-/intermediate-1-risk MDS patients. Although a survival benefit has been demonstrated in patients responding to ESA in two large retrospective trials, this still needs to be confirmed.[2,3] Currently, two prospective trials are ongoing to address this question. The Nordic MDS Group developed a decision model to define three groups of patients with different probabilities of response to ESA with or without G-CSF (*Figure 1*).[4] ESAs can be recommended in subsets of patients with MDS but to date, MDS remains an off-label indication for treatment with ESA and G-CSF.

The target haemoglobin level is 11.5g/dL. Suggested dosages for ESA are 30.000-60.000U of erythropoietin and 150-300$\mu$g darbepoetin per week. Response should be assessed after eight weeks. In case of insufficient erythroid response, the ESA dose can be increased or the addition of low-dose G-CSF may be considered. G-CSF is recommended to start at 300$\mu$g per week to a maximum of 3x300$\mu$g per week. In patients with RARS, low-dose G-CSF may be added to ESA from the beginning. If there is not at least a partial erythroid response after sixteen weeks, growth factor treatment should be stopped. In intermediate-2/high-risk patients, there are insufficient data to recommend use of haematopoietic growth factors.

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## Lenalidomide in del(5q) MDS

Partial or complete deletion of the long arm of chromosome 5 (del(5q)), with or without additional cytogenetic abnormalities is present in 10-15% of patients with *de novo* MDS, and is the most prevalent cytogenetic abnormality in MDS.[5] The '5q minus' syndrome represents a separate MDS subtype according to the World Health Organisation (WHO) classification. It typically affects women and is characterised by macrocytic anaemia, hypolobulated megakaryocytes, a normal or increased platelet count, mild neutropenia and less than 5% blasts in the bone marrow.[6] Del(5q) has historically been regarded as a marker of low-risk disease. However, it has nowadays been generally accepted that 'MDS with del(5q)' comprises a more heterogeneous group of patients with a variable prognosis, where the presence of additional chromosomal abnormalities or an elevated blast count is associated with an increased risk of transformation to AML and decreased overall survival.[7]

Lenalidomide has been shown to decrease the transfusion need in patients with MDS with del(5q) in large phase II (MDS 003) and phase III (MDS 004) trials. Lenalidomide is recommended for patients with IPSS low/intermediate-1-risk del(5q) MDS without additional cytogenetic abnormalities and who are red blood cell (RBC) transfusion-dependent. The recommended starting dose is 10 mg/day on day 1-21 of 28-day treatment cycles.[8] Response to treatment should be evaluated after the fourth cycle. Patients without any response after four cycles are unlikely to respond to lenalidomide and should be offered alternative treatment.[8,9] Lenalidomide is given until disease progression or unacceptable toxicity although treatment discontinuation can be considered in patients with transfusion-independence and complete cytogenetic response (CCR) on the condition that lenalidomide is continued for six months beyond CCR.[9] Currently the reimbursement of lenalidomide in Belgium is pending.

Myelosuppression is common but neutropenic fever or severe bleeding is rare. AML is a natural evolution of the disease and not predictable for individual patients. Progression to AML has to be monitored for all patients, including patients stopping the treatment. A bone marrow aspiration for morphology and cytogenetics is recommended every six months and/or in case of increasing cytopenia or appearance of circulating blasts.[9]

## Immunosuppressive treatments

There is increasing evidence that the cytopenias seen in MDS patients are in part due to immune mediated suppression by lymphocytes and monocytes. The considerable overlap between MDS and other immune mediated disorders, such as aplastic anaemia, has resulted in the introduction of immunosuppressive treatment strategies for patients with lower-risk MDS. Several trials have shown that approximately a third of patients with MDS respond to treatment with antithymocyte globulin (ATG) and/or cyclosporine A (CsA).[10] To date, only two prospective randomised trials on this subject have been reported. One published randomised phase II study compared horse and rabbit ATG in MDS and did not show clinically relevant differences.[11] The other multicentre prospective randomised trial demonstrated that horse ATG and CsA resulted in haematological improvement in a subset of patients, without impact on transformation-free survival and overall survival compared to best supportive care.[12]

Existing evidence indicates that immunosuppressive therapy is appropriate for patients with low/intermediate-1-risk disease who need treatment. Patients should have low (<5%) bone marrow blast count and no poor risk cytogenetics. Best candidates for this strategy are young patients (age <60 years), patients with hypocellular bone marrow, patients with a PNH clone, patients with trisomy 8 on cytogenetic analysis and patients that are HLA-DR15 positive. When this kind of treatment is considered, it should be performed soon after diagnosis since a short duration between diagnosis and treatment has been shown to improve outcome.[13] A large retrospective trial of 129 patients with MDS treated with immunosuppressives at the National Institute of Health, showed a better overall response rate for the combination of ATG and CsA (48%) compared to ATG (24%) or CsA (8%) alone. Additionally, responding patients had an improved overall survival and progression-free survival.[14]

## Transfusion and iron chelation

*Background*

The requirement of frequent RBC transfusions is a marker of poor prognosis in patients with MDS. The negative effect is most noticeable in low/intermediate-1-risk MDS.[15] One unit of packed cells contains 200-250 mg of iron and chronic transfusional support may lead to iron overload and secondary hemosiderosis. The benefit of iron chelation in MDS is unproven at this time and indirect support for the use of iron chelation therapy to prevent secondary hemosiderosis

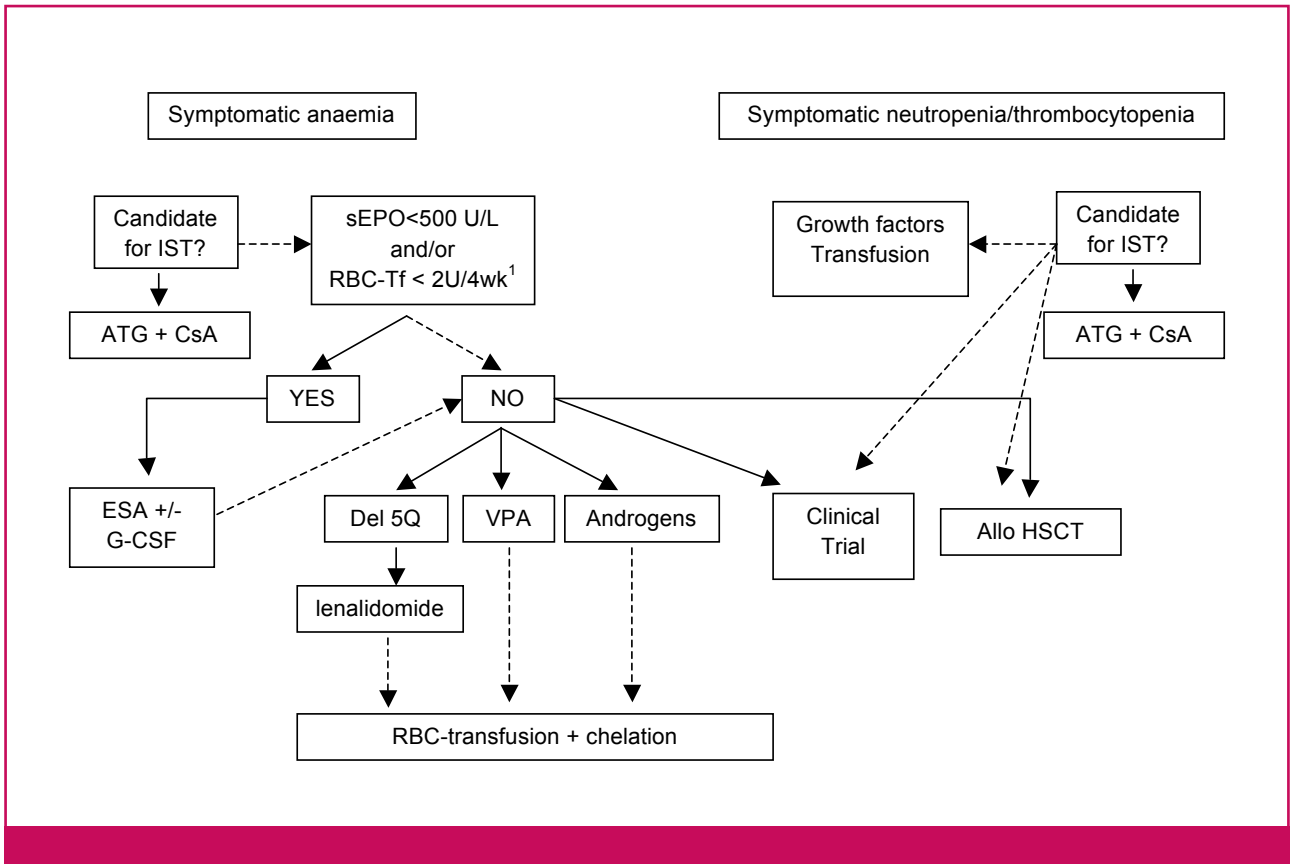


**Figure 1.** Treatment algorithm for Low/Int-1-risk IPSS.
Allo HSCT: allogeneic hematopoietic stem cell transplantation; ATG: anti-thymocyte globulin; CsA: cyclosporine A; EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; G-CSF: granulocyte-colony stimulating factor; RBC: red blood cell; VPA: valproic acid. [1]Nordic Score: RBC-transfusion need <2 units/month (1 point); sEPO < 500U/L (1 point). Probability of response to ESA is 74% (0 points), 23% (1 point), and 7% (2 points).[4]

in MDS comes from randomised studies in beta-thalassemia, where long term iron chelation reverses iron related organ damage, reduces morbidity and prolongs survival.[15] To support iron chelation therapy in MDS, the randomised double blind placebo controlled trial (TELESTO) of deferasirox in patients with low/intermediate-1-risk MDS and transfusional iron overload will answer most of the open questions. Iron overload is also associated with increased transplant related mortality in MDS patients undergoing allogeneic stem cell transplantation.[16] Retrospective studies suggest that iron chelation may improve the transplant-related mortality in iron overloaded patients.

*Recommendations*

In 2008, recommendations from a consensus working group on iron overload in MDS were published and these serve as a basis for the development of Belgian guidelines.[17] Body iron stores should be monitored at diagnosis and every three months thereafter in transfusion dependent MDS patients. Iron overload should be monitored using serum ferritin. In prospective studies of iron chelation a good correlation was found between serum ferritin and liver iron concentration, corroborating the use of regular serum ferritin assessments to monitor iron overload. Liver MRI is considered as useful but not essential.

The following MDS patients would benefit most from iron chelation:

- patients with serum ferritin levels >1000 ng/ml in the absence of inflammation or liver disease;
- transfusion dependent patients requiring two units per month or more for at least one year;
- patients with lower risk MDS (IPSS <1.5; WHO RA, RARS, del (5q));
- patients with a life expectancy of at least one year;
- patients without co-morbidities that limit prognosis;
- candidates for allograft;
- patients in whom there is a need to preserve organ function.

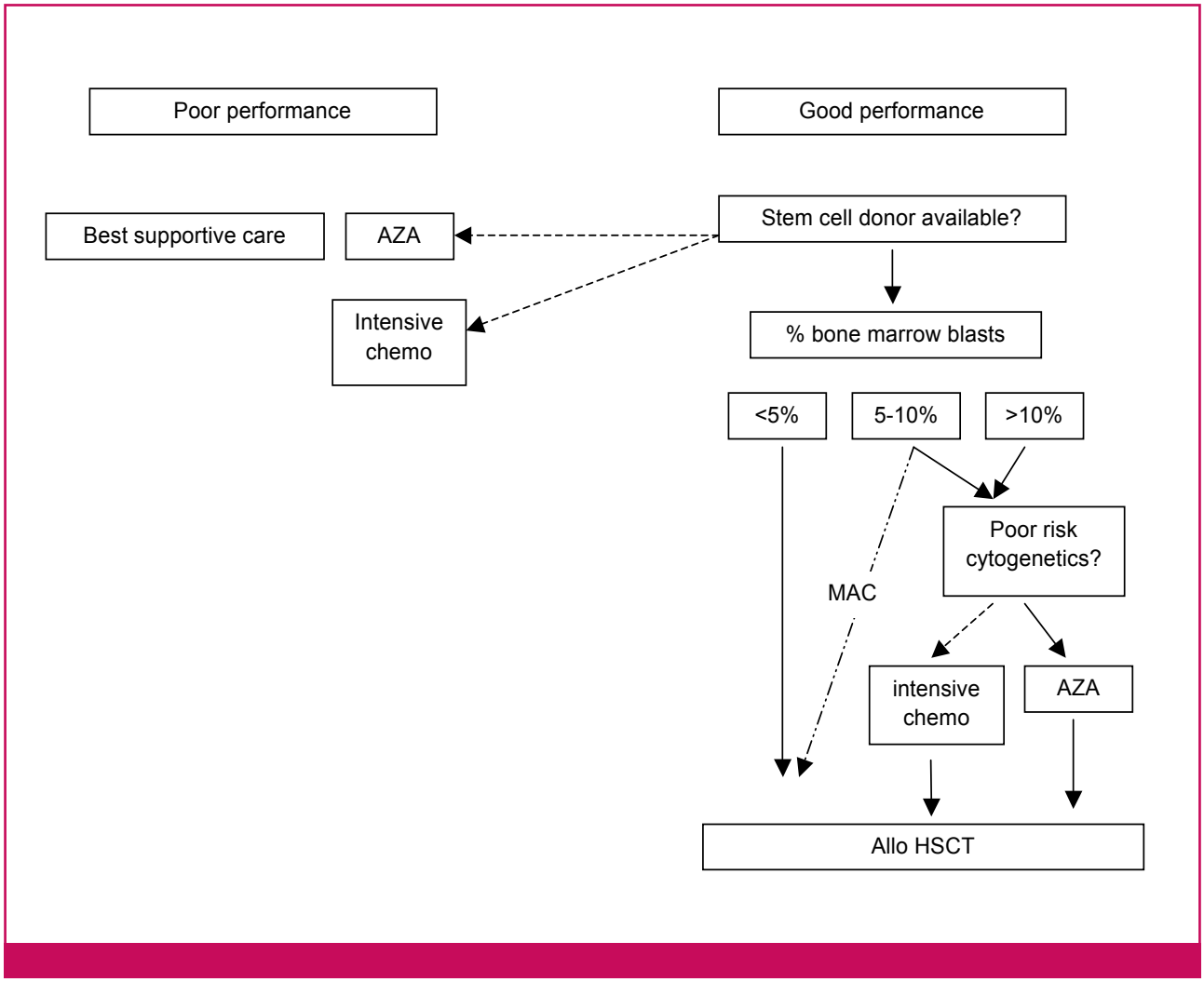


**Figure 2.** Treatment algorithm for Int-2/High-risk IPSS.
Allo HSCT: allogeneic hematopoietic stem cell transplantation; AZA: 5-azacitidine; MAC: myeloablative conditioning.

## Hypomethylating agents

Epigenetic modifications lead to differences in gene expression without alterations in DNA sequence. There is increasing evidence that DNA methylation, histone modifications and microRNA's are also involved in the clinical shaping of MDS. Changes in gene expression by epigenetic modifications are reversible and this has resulted in the use of methyltransferase-inhibitors (azacitidine and decitabine) and histone deacetylating agents for the treatment of MDS.

*Methyltransferase inhibitors: azacitidine*

Azacitidine has been extensively studied in MDS patients. Reimbursement is based on the results of the randomised controlled AZA-001 trial, comparing azacitidine to the three most commonly used treatments in higher risk MDS (best supportive care, low-dose cytarabine or intensive chemotherapy).[18] Median overall survival was significantly increased to 24.5 months for the azacitidine group versus 15.0 months for conventional care. The survival advantage was significant with azacitidine irrespective of marrow blast count (including patients with AML (20-30% BM blasts)), age (including patients >75 years) and cytogenetics (including patients with del(7)). Progression to AML was significantly delayed with azacitidine compared to conventional care.

Azacitidine is reimbursed for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation (HSCT) with:

- intermediate-2/high-risk MDS according to the IPSS;
- CMML with 10-29% marrow blasts without myeloproliferative disorder (i.e. <13.000/$\mu$L leucocytes);
- AML with 20-30% blasts and multi-lineage dysplasia, according to WHO 2008 classification.

Azacitidine is reimbursed only when used as first line treatment. Although there is a survival benefit irrespec-

tive of age, patients with a high MDS-CI co-morbidity score do not benefit from the treatment in terms of overall survival.

The probability of a response is predicted by performance status, the presence of peripheral blasts, cytogenetics and red blood cell transfusion need.[19] Patients with high-risk cytogenetics have a small chance of achieving complete remissions with intensive chemotherapy. In the AZA-001 trial, a high response rate was observed in patients with chromosome 7 abnormalities. Therefore the expert panel considers azacitidine the treatment of choice for patients with high risk cytogenetics as part of remission induction therapy prior to stem cell transplant. However, this is not possible under current reimbursement criteria.

The recommended starting dose for the first treatment cycle is 75 mg/m2 SQ for seven continuous days per 28-day treatment cycle, regardless of baseline blood values.[18] Peripheral blood counts can worsen during the first cycles of therapy and neutropenia and thrombocytopenia have to be monitored closely. Nausea is common and prophylactic 5-HT3 antagonists are reimbursed. Clinical responses do not occur immediately. Patients with at least haematological improvement or better after six cycles (i.e. reduction in transfusion need, transfusion independence, partial or complete response) should continue the treatment until unacceptable toxicity or disease progression. After one year of treatment (13 cycles) all patients require bone marrow evaluation.

## Intensive chemotherapy and stem cell transplantation

*Allogeneic hematopoietic stem cell transplantation in MDS*

To date, the only curative treatment for MDS is allogeneic hematopoietic stem cell transplantation (allo HSCT). Even when a complete remission can be obtained with intensive chemotherapy, the long term outcome without subsequent transplantation is poor. Therefore, when MDS is diagnosed in a patient, the first question to be answered is whether this patient is eligible for this kind of treatment. The introduction of reduced intensity conditioning (RIC) before allo HSCT has greatly extended the number of candidates for allografting. The decision for allografting avoids unnecessary therapies that could compromise the outcome of transplantation (e.g. transfusional iron overload) and provides adequate time for the search of a suitable donor.

*Timing of transplantation*

The recommendation to delay transplantation in low/intermediate-1-risk MDS and offer allo HSCT to patients with intermediate-2/high-risk MDS has largely been adopted by most transplant centres. This attitude is based on a pivotal, retrospective IBMTR study showing that for low/intermediate-1-risk MDS, maximal life expectancy was associated with delayed allo HSCT and that for intermediate-2/high-risk MDS, immediate allo HSCT was associated with maximal life expectancy.[20] Being transfusion-dependent or not appears to worsen outcome regardless of the therapy chosen. Although chelation therapy may change this paradigm, it seems appropriate to consider allo HSCT in patients with lower IPSS who become transfusion-dependent and do not respond to medical therapy. Patients with life-threatening thrombocytopenia or neutropenia are also candidates for immediate allografting, even with low-risk IPSS. Likewise, patients with adverse cytogenetics but preserved bone marrow function may be considered for allo HSCT even with an intermediate-1 IPSS score.

*Intensive chemotherapy before allogeneic HSCT*

Studies of intensive chemotherapy in patients with advanced stages of MDS report complete remission rates of about 60%.[21] However, remissions after chemotherapy usually last less than twelve months and the overall survival, especially in older patients, is modest. Chromosomal characteristics are important prognostic factors influencing remission rates. A recent donor versus no donor analysis of De Witte et al. shows that high-risk MDS patients with IPSS intermediate and poor risk cytogenetics have improved survival with allo HSCT after pre-transplant chemotherapy.[22] In MDS patients with good risk cytogenetics, there was no difference in survival between chemotherapy only and chemotherapy followed by allo HSCT.

The role of intensive chemotherapy in MDS remains a point of discussion and therefore no consensus recommendation can be made. From the data available, one may conclude that there is an advantage to try to aim for 5% or less blasts in the bone marrow before HSCT with pre-transplant chemotherapy.[23] MDS patients with favourable cytogenetics can have a good outcome with intensive chemotherapy without allo HSCT. Because of the lack of solid data, the best option is to treat MDS patients with intensive chemotherapy in the context of a clinical trial.

*Conditioning regimen (myeloablative versus reduced intensity)*

When feasible, a full conditioning is recommended. Most results published about HSCT in MDS are ob-

## Key messages for clinical practice

1. Adequate diagnosis and prognostication are key requisites for optimal treatment for patients with myelodysplastic syndromes.
2. The only curative treatment for myelodysplastic syndromes is allogeneic stem cell transplantation.
3. In lower-risk patients, response to erythropoiesis stimulating agents and immunosuppressive treatment has been shown to result in a survival benefit.
3. In higher-risk patients azacitidine has been shown to result in a survival benefit compared to supportive care.

tained in the context of total body irradiation (TBI) or busulfan (Bu) based full conditioning. For published series of RIC HSCT, there is much variability in conditioning protocols, in the post-HSCT strategy applied (donor lymphocyte infusion (DLI) or not, type and duration of the immune suppression) and also in the type of patient included. It is therefore very difficult to compare these results with a myeloablative approach in terms of relapse rate, transplant-related mortality and survival. But, it seems RIC HSCT can lead to a cure in a proportion of patients otherwise ineligible for a full conditioning. The lower treatment related mortality is counter-balanced by a higher relapse rate after RIC for advanced MDS.

## Conclusion

The choice of treatment is dependent on disease status, age and comorbidities. Therefore this decision should be made on an individual basis. To date the only curative treatment for MDS is allo HSCT which is a realistic option only in a minority of patients. Nevertheless, several other treatments have been shown to result in a survival advantage in selected patients and should therefore be considered. These include ESA's and immunosuppressive therapy in lower-risk patients and azacitidine in higher-risk patients.

## References

1. Meers S, Breems D, Bries G, et al. Management of myelodysplastic syndromes in adults: guidelines from the Belgian Haematological Society. Acta Clin Belg. 2013;68:253-62.

2. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol. 2008;26:3607-13.

3. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008;111:574-82.

4. Hellstrom-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997;99:344-51.

5. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol. 2012;30:820-9.

6. Van den Berghe H, Cassiman JJ, David G, et al. Distinct haematological disorder with deletion of long arm of no. 5 chromosome. Nature. 1974;251:437-8.

7. Mallo M, Cervera J, Schanz J, et al. Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia. 2011;25:110-20.

8. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood. 2011;118:3765-76.

9. Giagounidis AA, Kulasekararaj A, Germing U, et al. Long-term transfusion independence in del(5q) MDS patients who discontinue lenalidomide. Leukemia. 2012;26:855-8.

10. Meers S, Delforge M, Verhoef G. Het immuunsysteem bij myelodysplasie: a target for therapy? Ned Tijdschr Hematol. 2010;7:9-16.

11. Stadler M, Germing U, Kliche KO, et al. A prospective, randomised, phase II study of horse antithymocyte globulin vs rabbit antithymocyte globulin as immune-modulating therapy in patients with low-risk myelodysplastic syndromes. Leukemia. 2004;18:460-5.

12. Passweg JR, Giagounidis AA, Simcock M, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: a prospective randomised multicentre phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care--SAKK 33/99. J Clin Oncol. 2011;29:303-9.

13. Sauntharajah Y, Nakamura R, Wesley R, et al. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic

syndrome. Blood. 2003;102:3025-7.

14. Sloand EM, Wu CO, Greenberg P, et al. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol. 2008;26:2505-11.

15. Cappellini MD, Porter J, El-Beshlawy A, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica. 2010;95:557-66.

16. Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood. 2007;109:4586-8.

17. Bennett JM. Consensus statement on iron overload in myelodysplastic syndromes. Am J Hematol. 2008;83:858-61.

18. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10:223-32.

19. Itzykson R, Thepot S, Quesnel B, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood. 2011;117:403-11.

20. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104:579-85.

21. Ossenkoppele GJ, Graveland WJ, Sonneveld P, et al. The value of fludarabine in addition to ARA-C and G-CSF in the treatment of patients with high-risk myelodysplastic syndromes and AML in elderly patients. Blood. 2004;103:2908-13.

22. de Witte T, Hagemeijer A, Suciu S, et al. Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. Final results of a prospective randomised European Intergroup Trial. Haematologica. 2010;95:1754-61.

23. Warlick ED, Cioc A, Defor T, et al. Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant disease burden. Biol Blood Marrow Transplant. 2009;15:30-8.