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PRACTICE GUIDELINE

Optimizing outcomes with azacitidine: recommendations from Canadian centres of excellence

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ABSTRACT

Myelodysplastic syndromes (MDSS) constitute a heterogeneous group of malignant hematologic disorders characterized by marrow dysplasia, ineffective hematopoiesis, peripheral blood cytopenias, and pronounced risk of progression to acute myeloid leukemia. Azacitidine has emerged as an important treatment option and is recommended by the Canadian Consortium on Evidence-Based Care in MDS as a first-line therapy for intermediate-2 and high-risk patients not eligible for allogeneic stem cell transplant; however, practical guidance on how to manage patients through treatment is limited. This best practice guideline provides recommendations by a panel of experts from Canadian centres of excellence on the selection and clinical management of MDS patients with azacitidine. Familiarity with the referral process, treatment protocols, dose scheduling, treatment expectations, response monitoring, management of treatment breaks and adverse events, and multidisciplinary strategies for patient support will improve the opportunity for optimizing treatment outcomes with azacitidine.

KEY WORDS

Myelodysplastic syndrome, MDS, 5-azacitidine, Vidaza, clinical outcomes, practical recommendations, guidelines

1. INTRODUCTION

Myelodysplastic syndromes (MDSS) are frequently-occurring hematologic malignancies, affecting 3.3–4.5 people per 100,000 in North America and Europe[1]. Median age at diagnosis is 74[2]. Prognosis is commonly assessed using the International Prognostic Scoring System (IPSS), which divides patients into four risk groups according to number of cytopenias, marrow blast percentage, and marrow karyotype[3]. The scoring system was recently updated, but is not yet in widespread clinical use[4]. Individual treatment is dictated by the distinct pathologic and prognostic parameters of the various MDS subgroups. Patients in the higher-risk subgroups—namely, intermediate-2 (Int-2) and high-risk—have an increased risk of progression to acute myeloid leukemia (AML) and a median survival of 1.2 and 0.4 years respectively[3].

Although allogeneic stem-cell transplantation remains the only curative therapy for MDS[5,6], few MDS patients are candidates because of age, comorbidities, and absence of a suitable donor[7,8]. The years since the early 2000s have witnessed advances in MDS therapies aimed at improving the natural history of the disease and extending overall survival (OS). In particular, azacitidine has emerged as an important treatment option and is recommended by the Canadian Consortium on Evidence-Based Care in MDS as first-line therapy for Int-2 and high-risk patients[2].

The precise mechanism of action of azacitidine is unknown. Aberrant silencing of key genes, a reversible process that may occur through methylation, is thought to contribute to MDS pathogenesis[2]. Azacitidine is a pyrimidine nucleoside analog that inhibits DNA methyltransferase, thus resulting in a reduction of DNA methylation and altered gene expression that might, in turn, help to restore normal hematopoiesis[9]. Furthermore, induction of cytotoxicity might also be involved in the therapeutic effects of the drug[10].

Two key clinical trials demonstrated that azacitidine is superior to conventional care regimens. In 2002, Silverman *et al.*[11] reported results from the Cancer and Leukemia Group B 9221 study, a phase III randomized controlled trial comparing azacitidine with supportive care. Study patients receiving azacitidine experienced improved response rates and quality of life, a reduction in transfusion requirements, and a significant delay in progression to AML or death. Seven years later, the AZA-001 trial investigators reported significantly greater median OS in Int-2 and high-risk patients treated with azacitidine than with 3 commonly used conventional care regimens (24.5 months vs. 15 months respectively, $p = 0.0001$)[12].

After those initial reports, it became increasingly apparent that maximizing treatment duration is important for the best patient outcomes. Withdrawal of azacitidine treatment is associated with rapid loss of response[13]. Furthermore, in the AZA-001 trial, continuation of azacitidine treatment was associated with improvement from a first response of hematologic improvement to a higher response category of either partial response or remission (PR) or complete response or remission (CR) in almost half the responders, highlighting that continued therapy may enhance clinical benefit in higher-risk MDS[14]. Outlining best practices, such as treating until progression of disease, may lead to improved clinical benefit. The sections that follow outline best practice guidelines, recommended by a panel of experts from Canadian centres of excellence, aimed at optimizing outcomes using azacitidine in MDS patients.

2. STARTING TREATMENT

2.1 Referring Patients

Many patients with MDS are asymptomatic, and the diagnosis evolves after an abnormality is detected on routine complete blood cell count (CBC) or during a work-up for anemia[15]. We recommend that primary care physicians consider a diagnosis of MDS and refer patients for evaluation in instances of unexplained moderately severe or progressive cytopenias after reversible causes have been excluded. Cytopenias occurring in a high-risk situation—for example, in a patient who has previously received chemotherapy or in the context of another hematologic disorder—should be treated with particular urgency.

Additionally, primary care physicians should complete these tests before referral: CBC (peripheral smear), lactate dehydrogenase, reticulocyte count, iron (total iron binding capacity, ferritin), bilirubin, creatinine, alanine transaminase, alkaline phosphatase, vitamin B_{12}, and thyroid-stimulating hormone.

2.2 Who to Treat and When to Start Treatment

Once the diagnosis of MDS has been made and a risk status is ascertained, we advise beginning treatment as soon as possible. In patients with a high blast count (>10%) or poor-risk karyotype, urgency is advised. The Canadian Consortium on Evidence-Based Care in MDS recommends azacitidine "as first line therapy in all MDS patients with IPSS high-intermediate and high risk scores including WHO-defined AML (20–30% blasts) who cannot proceed immediately to allogeneic stem cell transplant. [Azacitidine] is not recommended as first line therapy in MDS patients with IPSS low and low–intermediate risk scores as there is no evidence that it alters the natural history of the disease nor is superior to standard therapy. The MDS consortium does not recommend combining [azacitidine] with other agents at this time outside the context of a clinical trial"[2].

We recommend azacitidine as first-line therapy in patients with higher risk MDS because such patients generally benefit from treatment with azacitidine in terms of life expectancy[9,16] and quality of life[17]. Moreover, those benefits are also seen in patients of advanced age[18]. Thus, treatment should be considered in most cases. However, deferral of azacitidine treatment can be considered in the face of significant comorbidity associated with an important decrease in life expectancy, very poor performance status (Eastern Cooperative Oncology Group 3–4), or marked frailty[19].

2.3 Initiating Dose and Length of Treatment

At treatment initiation, the recommended dose for all patients, regardless of baseline hematology values, is a subcutaneous injection of 75 mg/m^2 body surface area daily for 7 consecutive days every 28 days[16]. This treatment regimen is the only one to be associated with increased OS in a controlled clinical trial[12]. Because of treatment centre schedules, a dosing schedule of 5–2–2, in which patients receive 75 mg/m^2 daily for 5 days, followed by 2 days of no treatment (during a weekend), and then 2 more treatment days, is also widely used. The efficacy of the 5–2–2 dosing schedule has not been evaluated against the 7-day consecutive schedule in a prospective randomized controlled clinical trial, and survival data with that schedule are not currently available; however, the results of two studies appear to support use of this alternative[20,21].

We strongly recommend that patients be treated with azacitidine for a minimum of 6 months, and that in patients who achieve a documented response or stable disease (SD), treatment be continued until disease progression or unacceptable toxicity occurs. Azacitidine should not be stopped once patients achieve their personal maximal response, even in cases in which they continue in remission for a long period (that is, ≥12 months).

2.4 Initiating Dose in Special Populations

In the presence of renal impairment, patients on dialysis should be referred to a centre with extensive experience in the use of azacitidine. According to the prescribing information, no specific modification to the dose before starting treatment is recommended for patients with renal impairment (that is, baseline serum creatinine or blood urea nitrogen 2 or more times the upper limit of normal, or serum bicarbonate less than 20 mmol/L before treatment)[16]. However, if creatinine or blood urea nitrogen increases, or if serum bicarbonate decreases, the prescribing information suggests that, for the next cycle, the dose be reduced by 50% or delayed (or both) until values

return to normal or baseline. Recently, however, Douvali *et al.*[22] retrospectively analyzed IPSS Int-2 and high-risk MDS patients with normal renal function, mild renal insufficiency, and moderate renal insufficiency treated with azacitidine. Like Batty *et al.*[23], they reported comparable overall response rates and a similar median OS across all patient groups, independent of severity of renal insufficiency[22]. We therefore recommend, in cases of transient, unexplained elevations in serum creatinine or urea, revisiting the 50% dose reduction in the prescribing information after consultation with a centre with extensive experience, and monitoring the patient closely.

Patients with impaired liver function were excluded from the AZA-001 trial[12], and the prescribing information states that such patients should be treated with caution[16].

3. MANAGING TREATMENT

3.1 Physician Expectations of Treatment

Physicians should be treating patients, including patients with SD, until progression or loss of response. It also should be expected that blood counts may worsen with the first few cycles of treatment before improvement is seen. An early increase in platelet count has been reported to be a marker for later trilineage response and remission[24].

3.2 Monitoring Patients

Although most responders achieve a first response by treatment cycle 6, 48% of all responders experience continued improvement beyond the first response of hematologic improvement to a higher response category of either PR or CR. In fact, 92% of responders achieve their best response by cycle 12[14]. To monitor individual response rates and to customize cytopenia management strategies after treatment initiation, we suggest that a CBC be performed every 2 weeks during treatment cycles 1 and 2 and then consistently at the start of each subsequent cycle[14]. Additionally, tests for creatinine, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, and electrolytes are recommended at the beginning of each cycle.

We also propose that a bone marrow assessment be performed at 6 and 12 months, and again when progression or toxicity is suspected. Such testing allows for documentation of the individual's best response and provides valuable comparators for future analyses in the same individual.

3.3 Assessing Efficacy

In contrast to the AML chemotherapy paradigm, in which achievement of CR is a *sine qua non* of successful treatment, MDS patients treated with azacitidine whose best response is less than CR still receive a survival benefit. Analysis of data from the AZA-001 clinical trial established that azacitidine-treated patients achieving hematologic improvement without CR or PR experience a better OS than patients treated on conventional care regimens. Compared with progressive disease, SD is also associated with a significantly reduced risk of death[25]. We recommend that patients who achieve SD, PR, or CR should continue azacitidine treatment until disease progression.

3.4 Dose Adjustment and Management of Side Effects

The azacitidine prescribing information suggests dose adjustments for hematologic toxicity[16]. However, a survey of MDS experts in Canada, which was corroborated at the Canadian Conference on Myelodysplastic Syndromes 2012, showed that most physicians avoid dose reductions in practice. Although reduction avoidance is not currently grounded in evidence-based guidelines, we do not recommend dose reductions and suggest that the first 6 months of azacitidine treatment be viewed as similar to induction therapy. Thus, during the first 6 cycles, treatment should continue even in the face of new or severe cytopenias, although increased transfusion support and monitoring for risks associated with neutropenia might be required. We propose that dose reductions are required only very rarely and that dose delays should occur only under exceptional circumstances—such as in the presence of severe infections—and not because of hematologic adverse events (AEs). For more information, consult the azacitidine product monograph[16].

Prophylactic platelet transfusions are best when individually tailored to patient risk; they should be given to support patients who have severe or symptomatic azacitidine-induced thrombocytopenia. Although no evidence-based transfusion threshold has been defined in this population, prudence suggests considering transfusion if the patient's platelet count falls below 10×10^9/L or if a lesser degree of thrombocytopenia is accompanied by clinically significant bleeding.

In general, we do not recommend routine use of granulocyte colony–stimulating factor (G-CSF) as primary prophylactic therapy for febrile neutropenia. In terms of managing AEs in very elderly patients, no specific recommendations have been made. Those patients should be treated as others are.

3.5 Treatment Breaks

We recommend against treatment breaks: the literature and clinical experience suggest that stopping treatment ultimately results in loss of response. Rates of response upon re-treatment are lower than for primary treatment, and second responses, when achieved, are typically of shorter duration. Voso *et al.*[13] recently reviewed outcomes in 13 patients who,

while still responding, discontinued azacitidine because of comorbidities, infections, and patient choice. They reported that most patients rapidly relapsed, with a median time to progression of 5.4 months. Furthermore, Ruter *et al.*[26] found that re-treatment with the hypomethylating agent decitabine in patients with MDS resulted in a decrease in the quality and duration of secondary responses. The length of a treatment hiatus that is too long is currently unknown.

Nevertheless, physicians must be sensitive to the potential burden borne by some patients on azacitidine therapy, particularly the restrictions that their treatment may impose on travel. If a patient insists on a treatment break, we advise that they be counselled to ensure that they fully understand that treatment breaks are not recommended, given that their subsequent treatment options are quite limited. Options can include stem-cell transplantation (for which few patients are eligible), re-treatment with azacitidine (on the understanding that the chance of a response is greatly decreased), a clinical trial, and supportive or palliative care.

3.6 Concomitant Treatment

In patients treated with azacitidine, we do not recommend primary prophylactic use of G-CSF (because of the increased risk of blast growth) or antibiotics (because of the potential for development of resistance)[27]. If primary prophylaxis against infection is being considered, we prefer the use of antibiotics to G-CSF in most situations. Secondary prophylactic use of G-CSF or antibiotics might be warranted in cases in which severe infection, sepsis, or admission to an intensive-care unit has previously occurred[12].

Anti-emetics such as ondansetron or granisetron should be used prophylactically in all patients before each treatment. Metoclopramide can be a useful anti-emetic in cases of intolerance to 5-HT_3 antagonists. The severity of azacitidine-induced nausea is variable, and so the dose and type of anti-emetic agent should be adjusted to the individual patient's requirements and symptoms. Because 5-HT_3 antagonists can cause constipation, patients should also be prescribed a laxative during their treatment week. In addition to pharmacologic agents, flax seeds (approximately 5 tablespoons daily) are found by many patients to be helpful in that regard.

Although local injection site reactions are typically mild with ideal injection technique, some patients experience significant inflammation and discomfort. Cool compresses and topical applications of evening primrose oil immediately after injection often ameliorates those symptoms[28]. Severe injection site reactions are rare; however, secondary cellulitis is a possibility, especially in neutropenic individuals. In patients with severe or persistent pain and erythema at the injection site, the possibility of infection should be considered, and appropriate antibiotic therapy should be initiated.

4. TALKING TO PATIENTS

4.1 Discussing Treatment Initiation

At the beginning of treatment, a multidisciplinary team approach helps to provide a continuum of care through the diagnosis, treatment, and monitoring phases of MDS. In addition to the involvement of a diverse group of health care professionals (including family practitioners, hematologists, oncologists, and nurses), family and friends often play an active role in building a support system for patients. Open communication between these parties about the treatment process will empower patients to participate in the decision-making process for their care[29].

We propose that the first step should be to communicate clearly to the patient that Int-2 or high-risk MDS is a serious condition associated with decreased OS and rapid progression to AML[3]. Because disease progression is inevitable, physicians should stress the importance of receiving immediate treatment.

4.2 Successfully Managing Patient Expectations

We suggest that physicians ensure that patients and their families have realistic expectations about the treatment course, duration, and outcome. The important message that treatment duration will be a minimum of 6 months, and that it should continue as long as the benefit continues or until the disease progresses, must be communicated at the outset. Patients should also have a clear understanding that treatment with azacitidine is not curative and that treatment failure will eventually occur. Instead, the purpose of treatment is to improve bone marrow function and stabilize disease, which will help to improve life expectancy and delay progression to AML[16].

Physicians should disclose to patients the nature, duration, and management of the AEs that may occur during azacitidine treatment, including cytopenias, neutropenia, nausea, gastrointestinal events, and injection site reactions[2]. Treating with azacitidine through cytopenias can mean that patients will feel worse before they feel better; however, most AEs will eventually subside in frequency as treatment continues[30]. Thus, setting AE expectations before and during treatment can proactively address patient concerns and forestall patients from discontinuing therapy before achieving maximum benefit. Treatment compliance, in terms of attending routine follow-ups that monitor condition and response, should also be discussed with patients, given that compliance is an important determinant of health status and quality of life.

4.3 Signs of Response

Studies have shown that good responses to treatment involve major improvements in blood counts and decreased need for transfusions[11,12]. Indeed, an early

jump in platelet count often presages response[24]. Moreover, with azacitidine, patients experience significant improvement in physical functioning, fatigue, dyspnea, psychological distress, and overall quality of life[17].

4.4 Access to MDS Treatment Centres

Starting treatment is a personal decision that patients, especially those not near a treatment centre, must make by weighing the benefits of treatment against the cost and time challenges of receiving treatment far from home. As discussed, the benefits of azacitidine treatment can be substantial for the patient, potentially including longer survival, less dependence on transfusion, and delayed progression to AML.

4.5 Patient Education

Education for patients and health care providers should be a priority at MDS treatment centres. Patient support materials should include information on treatment administration, potential AEs, toxicities, and prognosis. Moreover, education in these areas for general practitioners in oncology, pharmacists, and nurses is crucial so that patients receive clear, consistent messages across all disciplines.

4.6 Patient Services

Several support programs that provide social services, financial assistance, support group meetings, and other up-to-date information related to MDS are available to Canadian patients and caregivers. The Aplastic Anemia and Myelodysplasia Association of Canada (http://www.aamac.ca), the MDS Foundation (http://www.mds-foundation.org), and the Leukemia and Lymphoma Society of Canada (http://www.llscanada.org) are three such resources that offer these essential services and to which patients can be referred.

5. CONCLUSIONS

With two clinical trials demonstrating that azacitidine is superior to conventional care regimens[11,12], azacitidine has emerged as an important option in the treatment of MDS. The key objective of the guidelines presented here is to outline best practices in the use of azacitidine to treat MDS, with the ultimate goal of improving clinical benefit for patients through treatment until disease progression.

In summary, treatment should begin as soon as possible after diagnosis. Azacitidine is recommended as first-line therapy for Int-2 and high-risk MDS, except in patients proceeding immediately to stem-cell transplantation. Patients, including the elderly, benefit from azacitidine therapy in terms of life expectancy and quality of life; only in very rare cases should treatment deferral be considered. Azacitidine as first-line treatment for patients with low and low–intermediate MDS is not recommended.

An initial subcutaneous dose of 75 mg/m^2 body surface area daily for 7 consecutive days every 28 days is recommended. If required, a 5–2–2 dosing schedule might be acceptable, although no randomized, controlled clinical trial investigating the efficacy of that schedule with respect to survival has been conducted. Patients should be treated with azacitidine until disease progression or unacceptable toxicity occurs; treatment should not be stopped once a patient achieves remission. Keep in mind that, with treatment, blood counts will often get worse before they improve. Regular monitoring, including CBC and bone marrow assessments, should occur throughout treatment.

Dose reductions are not recommended, and treatment should continue despite new or severe cytopenias, although this recommendation is not grounded in current evidence-based guidelines. Only in exceptional circumstances (such as severe infection) should dose reductions or delays occur. Treatment breaks are also not recommended, given that once a response is lost, the rate of response upon re-treatment is less.

Anti-emetics should be used prophylactically in all patients before treatment commences. Primary prophylactic use of G-CSF and antibiotics is generally not recommended, but secondary prophylactic use may be warranted in cases in which the patient has previously experienced severe infection. Patients should be counselled that MDS is a serious condition associated with decreased life expectancy and rapid progression to AML, and thus immediate treatment is important and necessary. It should be made clear to patients that azacitidine is not curative and that they will receive treatment until loss of response or disease progression. Patients should also be counselled regarding the nature, duration, and management of expected AEs before starting treatment.

If instituted, these best practice guidelines recommended by a panel of experts from Canadian centres of excellence can potentially enhance the clinical benefit of azacitidine treatment in patients with MDS.

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8. REFERENCES

1. Nguyen PL. The myelodysplastic syndromes. *Hematol Oncol Clin North Am* 2009;23:675–91.
2. Buckstein R, Yee K, Wells RA on behalf of the Canadian Consortium on Evidence-Based Care in MDS. 5-Azacytidine in myelodysplastic syndromes: a clinical practice guideline. *Cancer Treat Rev* 2011;37:160–7.
3. Greenberg P, Cox C, LeBeau MM, *et al.* International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079–88.
4. Greenberg PL, Tuechler H, Schanz J, *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012;120:2454–65.
5. Abel GA, Koreth J. Optimal positioning of hematopoietic stem cell transplantation for older patients with myelodysplastic syndromes. *Curr Opin Hematol* 2013;20:150–6.
6. Koreth J, Pidala J, Perez WS, *et al.* Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with *de novo* myelodysplastic syndromes: an international collaborative decision analysis. *J Clin Oncol* 2013;31:2662–70.
7. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes.* Ver. 2.2014. [Available online at: http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf (free registration required); cited December 19, 2012]
8. Sekeres MA, Schoonen WM, Kantarjian H, *et al.* Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. *J Natl Cancer Inst* 2008;100:1542–51.
9. Raj K, John A, Ho A, *et al. CDKN2B* methylation status and isolated chromosome 7 abnormalities predict responses to treatment with 5-azacytidine. *Leukemia* 2007;21:1937–44.
10. Khan R, Schmidt–Mende J, Karimi M, *et al.* Hypomethylation and apoptosis in 5-azacytidine-treated myeloid cells. *Exp Hematol* 2008;36:149–57.
11. Silverman LR, Demakos EP, Peterson BL, *et al.* Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. *J Clin Oncol* 2002;20:2429–40.
12. 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.
13. Voso MT, Breccia M, Lunghi M, *et al.* Rapid loss of response after withdrawal of treatment with azacitidine: a case series in patients with higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia. *Eur J Haematol* 2013;90:345–8.
14. Silverman LR, Fenaux P, Mufti GJ, *et al.* Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. *Cancer* 2011;117:2697–702.
15. Barzi A, Sekeres MA. Myelodysplastic syndromes: a practical approach to diagnosis and treatment. *Cleve Clin J Med* 2010;77:37–44.
16. Celgene Inc. *Vidaza: Azacitidine for Injection, 100 mg Azacitidine per Vial* [product monograph]. Mississauga, ON: Celgene Inc.; 2012.
17. Kornblith AB, Herndon JE 2nd, Silverman LR, *et al.* Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. *J Clin Oncol* 2002;20:2441–52.
18. Seymour JF, Fenaux P, Silverman LR, *et al.* Effects of azacitidine compared with conventional care regimens in elderly (≥75 years) patients with higher-risk myelodysplastic syndromes. *Crit Rev Oncol Hematol* 2010;76:218–27.
19. Rockwood K, Song X, MacKnight C, *et al.* A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
20. Garcia R, De Miguel D, Bargay J, *et al.* Effectiveness of various dosage regimens of azacitidine in patients with myelodysplastic syndromes: safety and efficacy final data from the Spanish Azacitidine Compassionate Use Registry [abstract 1853]. *Blood* 2010;116:772.
21. Lyons RM, Cosgriff TM, Modi SS, *et al.* Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Oncol* 2009;27:1850–6.
22. Douvali E, Papoutselis M, Vassilakopoulos TP, *et al.* Safety and efficacy of 5-azacytidine treatment in myelodysplastic syndrome patients with moderate and mild renal impairment. *Leuk Res* 2013;37:889–93.
23. Batty GN, Kantarjian H, Issa JP, *et al.* Feasibility of therapy with hypomethylating agents in patients with renal insufficiency. *Clin Lymphoma Myeloma Leuk* 2010;10:205–10.
24. van der Helm LH, Alhan C, Wijermans PW, *et al.* Platelet doubling after the first azacitidine cycle is a promising predictor for response in myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML) patients in the Dutch azacitidine compassionate named patient programme. *Br J Haematol* 2011;155:599–606.
25. Gore SD, Fenaux P, Santini V, *et al.* A multivariate analysis of the relationship between response and survival among patients with higher-risk myelodysplastic syndromes treated within azacitidine or conventional care regimens in the randomized AZA-001 trial. *Haematologica* 2013;98:1067–72.
26. Ruter B, Wijermans PW, Lubbert M. Superiority of prolonged low-dose azanucleoside administration? Results of 5-aza-2′-deoxycytidine retreatment in high-risk myelodysplasia patients. *Cancer* 2006;106:1744–50.
27. Sloand EM, Yong AS, Ramkissoon S, *et al.* Granulocyte colony–stimulating factor preferentially stimulates proliferation

of monosomy 7 cells bearing the isoform IV receptor. *Proc Natl Acad Sci U S A* 2006;103:14483–8.
28. Platzbecker U, Aul C, Ehninger G, Giagounidis A. Reduction of 5-azacitidine induced skin reactions in MDS patients with evening primrose oil. *Ann Hematol* 2010;89:427–8.
29. Kurtin SE, Paterson P, Wintrich S, *et al.* Patient and family resources for living with myelodysplastic syndromes. *Clin J Oncol Nurs* 2012;16(suppl):58–64.
30. Santini V, Fenaux P, Mufti GJ, *et al.* Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*. *Eur J Haematol* 2010;85:130–8.

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