

PREVENTING INFECTIONS IN HIGHER-RISK MYELODYSPLASTIC SYNDROME PATIENTS TREATED WITH HYPOMETHYLATION AGENTS

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Disclosure: No potential conflict of interest.

Citation: EMJ Hema. 2013;1:58-63.

ABSTRACT

Hypomethylation agents became the standard of care for patients with high-risk myelodysplastic syndrome (MDS). While long-term benefits of azacitidine (AZA) and decitabine (DEC) were demonstrated in multiple studies, methods to enhance patients' safety during therapy with those agents are pending. The causative correlations between drug administration and non-life threatening complications such as injection-site erythema or gastrointestinal (GI) discomfort are obvious. However, infections, which are the most common life-threatening complication among higher risk MDS patients, are frequent even in those receiving therapy other than hypomethylation agents, including supportive care solely. Therefore, the contribution of hypomethylation therapy to infection risk is difficult to determine. Herein, data regarding infectious complications, their prevalence, risk stratification, and methods of prevention will be reviewed.

Keywords: Myelodysplastic syndrome, azacitidine, infections, prophylaxis.

INTRODUCTION

Myelodysplastic syndrome (MDS) is often referred to as a preleukaemic condition. However, only in a minority of patients, MDS transforms into leukaemia. The natural history of MDS is best described by observational studies conducted prior to the introduction of hypomethylation agents. Indeed, among patients in whom causes of death were recorded, infection or bleeding resulting from bone marrow failure were reported to be the main causes of deaths, while leukaemic transformation was much less prevalent.^{1,2} In the era of hypomethylation therapy, most patients with higher risk MDS receive prolonged therapy. 3 to 6 or even 12 cycles of therapy with azacitidine (AZA) or decitabine (DEC), are required to achieve the maximal beneficial effect.³⁻⁶ Ensuring patients' safety during this prolonged therapy is essential. Therefore, development of protocols aiming to prevent potential serious infections and other complications while awaiting clinical response is desired. Although no prospective randomised trials have been conducted and no guidelines

are available,⁷ the data which are accumulating are enabling the identification of patients with the greatest risk for infection, and evaluating the efficacy of different potential methods for infection prevention.

HYPOMETHYLATION EFFECT AND INFECTION

Therapies available for higher risk MDS patients can be divided into disease modifying and palliative. Currently, apart from intensive chemotherapies and allogeneic stem cell transplantation (Allo-SCT), which are beyond the scope of this review, the disease modifiers that are widely in use in MDS are AZA and DEC. The most hazardous side effect of hypomethylation agents is their effect on haematopoiesis. Pancytopenia, including neutropaenia, is often worsened following AZA or DEC initiation. In major prospective trials, the prevalence of neutropaenia increased from 76% to 91% in AZA-treated patients⁸ and from 35% to 47% in patients receiving DEC.⁹ Surprisingly, most studies

reported that the infection rate in patients treated with hypomethylation agents, although prominent, was not higher than the parallel prevalence in the untreated higher risk MDS patient population.⁸⁻¹² Yet, these statements describe the total infection rate throughout the whole follow-up period and should be further dissected. It is imperative to take into account that the timeline of infectious events differs between groups. Higher risk MDS patients, receiving none or palliative therapy, deteriorate over time and infections are more customary later in the disease course. In contrast, most patients on hypomethylation agents experience a transient decrease in blood counts following the first cycles of therapy, which may improve over time. Multiple studies confirmed that, while on hypomethylation therapy, infection risk is very high during the first two-three cycles of therapy and it substantially decreases thereafter.¹³⁻¹⁵ Thus, although hypomethylation agents are not associated with an increase in total infection burden, during palliative therapy infections are often associated with progression of the underlying disease, while during hypomethylation therapy infections occur earlier and should be considered drug-related. Multiple mechanisms may be accountable for immune suppression during hypomethylation therapy. One mechanism is related to the decrease in neutrophil count yet, hypomethylation leads to changes in expression levels of genes that may alter immune function. The immunomodulating effect of hypomethylation agent was demonstrated both in mice¹⁶ and in humans,¹⁷ and an increase in T-cell regulatory activity was reported. DEC was shown to facilitate immunosuppression in the context of innate immune response.¹⁸ Overall, hypomethylation therapy triggers complicated processes and its effect on the immune system is behind its direct effect on neutrophil count.

Identifying MDS Patients with the Highest Risk for Infection

Most studies reporting the outcome of AZA and DEC therapy elaborated on drug efficacy and their haematological effects in various patient populations, but only briefly described infectious complications. Even the response criteria in myelodysplasia, issued in the year 2000 and revised in 2006,^{19,20} includes just a general statement that a neutrophil level lower than $1,000 \times 10^9/L$ may serve as an acceptable cut-off for infection risk. This cut-off was suggested based on acceptable discrimination in leukaemia patients and not on solid evidence obtained in MDS patients. The first work to identify risk factors for infection

during AZA therapy was a retrospective Israeli survey with a high national coverage. It included 97% of all higher risk MDS/acute myeloid leukaemia (AML) patients treated with AZA in Israel during a 3-year period.¹⁵ Data of 928 treatment cycles prescribed to 184 patients were recorded. Infection rate was 16.5%, three-quarters of events required hospitalisation, and about one-fifth were fatal. In multivariate analysis, only low haemoglobin level, low platelet count, and unfavourable cytogenetics were found to predict infection. Prior to each cycle, poor cytogenetics and a platelet count below $20 \times 10^9/L$ are most predictive of infection development. Although a neutrophil count below $500 \times 10^9/L$ is also associated with infection, some patients may experience multiple infections even if their neutrophil counts are normal, while others live well suffering from no infections despite a prolonged neutropaenia. Infection risk is likely to be related to the reserves of the bone marrow (BM) and its ability to respond to early signs of microorganism invasion, which does not always correlate with peripheral neutrophil count. Poor cytogenetics and low platelet count may be associated with poorer BM reserves. It was reported that favourable cytogenetics and a rise in thrombocyte count during AZA therapy predict a good haematological response and a longer survival.²¹ This is the other side of the same coin. Cytogenetics and platelet counts represent the BM potential for better (response) or for worse (infection).

Definition of Infection and Common Causative Germs

Studies in MDS patients reported different incidence of infection and a wide spectrum of outcomes. This may be explained by variation in MDS severity among participants in different studies and by diverse criteria of infection recognition. Table 1 summarises the studies reporting infection incidence, while most of them ignored the infection outcome. In addition, although many of the patients who progressed to AML during therapy succumbed to infection, it is difficult to reveal in some studies whether those patients were considered among infection-complicated patients or not. Data regarding types of microorganisms and syndromes affecting higher risk MDS patient during hypomethylation therapy are scarce. Available information suggests that bacterial infections are responsible for the vast majority of infectious events during hypomethylation therapy.¹⁵ Clearly, MDS patients are immunosuppressed and prone to various types of opportunistic infections. Invasive fungal infections also deserve attention,

Table 1. Infection incidence during hypomethylation therapy.

Type of Study	Number of Participants	AZA or DEC	Incidence	Outcome (Death Rate)	Reference
Prospective	99	AZA	20%	NR	(34)
Prospective	179	AZA	0.6 per patient-year	NR	(8)
Prospective	66	DEC	27%	7%	(11)
Prospective	89	DEC	28%	NR	(35)
Prospective	95	DEC	1%	NR	(27)
Retrospective	38	AZA	29%	18%	(36)
Retrospective	184	AZA	16.5%	20%	(15)

yet, information regarding their incidence is scarce and this issue requires a well-designed, prospective follow-up study, outfitted with appropriate CT scans and galactomannan monitoring, similar to those performed in AML or post Allo-SCT patients.

Infection prevention should be focused on the most common and/or dangerous germs. Tailoring infection prevention methods requires a clear recognition of the nature of infectious events. In higher risk MDS patients treated with hypomethylation agents, risk factors (poor cytogenetics and low thrombocyte prior to therapy), the most vulnerable period of time (first two or three cycles), and the commonest infectious germs (common bacteria) should be the basic parameters to be taken into account while developing prophylaxis protocols.

Methods for Infection Prevention During Hypomethylation Therapy

General prevention methods

Higher risk MDS patients are prone to infection due to multiple defects in the immune system function. Not only are many of the patients neutropaenic, but defects in the normal function of neutrophils, B, T and NK cells, and iron overload, if present, may all alter response to microorganism invasion.⁷ It is therefore highly important to educate patients and their families on standard precautions according to the customary local protocol. Hand hygiene, avoidance of close contact with people suffering from contagious diseases, and vaccination of family members should be encouraged. Patients should be urged to immediately contact their primary treating physician or local health care facilities in case of fever or early signs of infection, using an efficient communication channel.

Growth factors (G-CSF or GM-CSF)

The rationale for using myeloid growth factor in higher risk MDS patients is based on extrapolation of data obtained from other neutropaenic settings, which are often related to chemotherapy. There are no studies evaluating the potential benefits of simultaneous usage of hypomethylation agent and myeloid growth factors. The only data available are derived from studies in higher risk MDS patients treated with chemotherapy^{22,23} or from observational studies;²⁴ none of them demonstrated a survival benefit. Thus, the major drawback from the usage of G-CSF or GM-CSF, in the context of MDS, is lack of evidence for its effectiveness. Physicians commonly express fear from facilitating leukaemic transformation by growth factors. However, such apprehension is also not supported by evidences. Moreover, safety of G-CSF or GM-CSF usage in AML was demonstrated by 18 controlled studies.²⁵ Until the firm benefits of reducing infection and hospitalisation or prolongation of survival can be demonstrated, the rise in neutrophil counts, resulting from growth factors administration, does not necessarily argue for its routine concomitant prophylaxis administration during hypomethylation therapy.

Antibiotic prophylaxis

Routine prophylaxis application of antibiotics in neutropaenic patients is debatable. Knowledge of the epidemiology and prevalence of different microorganisms generating infections in higher risk MDS patients is essential for determination of a preferred antibiotic prophylaxis protocol. Microbiology data is scarcely available, and in many studies patient microbiological evaluation was incomprehensive. With this limitation in mind, existing data suggest that bacterial infections are

most prevalent and responsible for the majority of infection-related deaths of higher risk MDS patients.⁷¹⁵ Usage of anti-mould or anti-viral agents cannot be routinely recommended outside of clinical trials but antibacterial prophylaxis may be justified.

Currently, fluoroquinolone prophylaxis is recommended for a limited group of cancer patients who become neutropaenic after chemotherapy. Duration and profoundness of neutropaenia are the main parameters used to justify antibiotic prophylaxis in these patients.^{26,27} However, as discussed above, in higher risk MDS patients, neutropaenia is not the most powerful factor associated with infection risk. Yet, in a small retrospective study of 28 patients receiving DEC, prophylaxis with antibiotics and G-CSF was reported to decrease the rate of infections during therapy.²⁸ However, not only is this study small and retrospective, but even the antibiotic protocols vary among patients within this trial. Notably, the likelihood for emergence of resistant bacteria in patients' flora and within the institution environment increases with prolonged antibiotic prophylaxis. Thus, the use of prophylactic antibiotic protocols during prolonged hypomethylation therapy should be targeting local microbiological flora, restricted to the most fragile patients throughout the highest risk periods only.

Hypomethylation agent dose

Possible correlations between AZA or DEC doses and infection rates are difficult to reveal. In our large retrospective study, we reported that a reduced dose of 75 mg/m² for 5 days was prescribed in about one-third of the reported 928 AZA cycles. A history of previous infection, non-haematological co-morbidities, and advanced age are among the reasons considered by doctors when AZA therapy is decided upon. To untangle the potential connection between a previous infection and the following AZA dosage which may alter the ability to evaluate the dose effect of hypomethylation agents on infection risk, we limited the analysis to the data of the initial AZA cycle prescribed to our group of 184 patients. Interestingly, even though the dominant specific factor that drove physicians to decrease the AZA dose was not identified, characteristics of the patients receiving a full AZA dose of 75 mg/m² for 7 compared to 5 day cycles were similar; lowering the AZA dose significantly reduced infection risk.²⁹

Hypomethylation agents are spreading rapidly as the treatment of choice for higher-risk MDS patients. Infections are the leading cause of early mortality during therapy and therefore the importance of infection prevention could not be underestimated. In the absence of solid evidence, practical prophylaxis policy should rely on the following principles. First, prospective studies of prophylaxis protocols should be encouraged. Endeavours should be focused on patients with the highest risk for infection, such as those who present with low platelet counts and poor cytogenetics, especially during the first two cycles of hypomethylation therapy. Outside of clinical trials, all patients and families should receive detailed and comprehensive instructions regarding general prevention methods (e.g. hand hygiene, vaccines, isolation policy, etc). Patients should be monitored for early signs of infections and evaluated for comorbidities that may aggravate the infection risk (e.g. chronic lung disease, diabetes, peripheral vascular disease). Advanced age and a moderate elevation in creatinine level do not increase the risk for infection and do not justify prophylaxis or reduction of hypomethylation agent dose. Prophylaxis is advised for patients presenting with poor cytogenetics or with a platelet count lower than 20,000 cell/mcl prior to AZA administration, especially during the first two cycles of therapy. Fluoroquinolones, G-CSF and even a decrease in AZA dose may lower the infection rate.

Since no studies comparing the efficiency of these methods are available, recommendations are based on speculative estimation of benefits and adverse effects. Many physicians hesitate to use G-CSF in higher risk MDS patients due to its potential effect on blast proliferation, although even in leukaemic patients, G-CSF administration did not increase relapse rates.³⁰ The issue of whether reducing hypomethylation dose may alter the drug efficacy is still debatable,^{31,32} and in a large study aiming for the establishment of AZA response predicting score, both reduced and standard AZA doses yielded identical response rates (41% versus 44%).³³ Yet, the initial two cycles of low-dose hypomethylation agents followed by full-dose cycles in patients recognised as prone to infection is a protocol that should be prospectively evaluated. Currently, it is likely that a time-limited antibiotic usage, restricted to patients at high risk, confined to the first two cycles of therapy, may lead to the highest benefits at the lower adverse cost.

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