Tratamiento estándar de los síndromes mielodisplásicos adaptados al riesgo

Risk-adapted standard treatment of myelodysplastic syndromes

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Abstract

Treatment of MDS has since many years been based mainly on conventional risk scores dividing patients into lower and higher-risk MDS. During recent years the fast development of knowledge about mutational profiles has added significantly to the decision-making and has also fostered development of novel targeted drugs in myeloid malignancies. Moreover, the possibilities to guide patients through the hitherto only curative therapeutic option, allogeneic stem cell transplantation, have improved markedly. Hence NGS sequencing is today affecting diagnostics, prognostication, and choice of treatment, as well as the tools for detection of minimal residual disease, and will develop to a natural part of future patient management.

Introduction

The myelodysplastic syndromes (MDS) constitute a heterogeneous group of myeloid malignancies originating in the hematopoietic stem and progenitor cell compartment (HSPC), an established statement that not until recently has been scientifically validated in MDS[1-3].

The cellular origin of the disease, as well as the molecular disease mechanisms leading to specific disease phenotype and patient symptoms is, however, utterly important for the choice of treatment and for the development of novel therapeutics.

Classical low-risk MDS subtypes including 5q-syndrome and MDS with ring sideroblasts (MDS-RS, according to WHO 2016 classification[4]) arise in rare phenotypically intact multipotent hematopoietic

stem cells (HSC).

These initiating cancer stem cells can subsequently be subject to acquisition of additional mutations leading to altered disease phenotype including disease progression. Interestingly, the risk of clonal evolution seems to be more frequent in del(5q) MDS[5] than in MDS-RS and some other low-risk subtypes, which needs to be considered when long-term treatment is planned, including evaluation for potentially curative allogeneic stem cell transplantation (SCT)[5].

Higher-risk MDS subtypes are usually characterized by compromised HPSC phenotypes, as recently shown in a study of MDS with cytogenetic alterations encompassing chromosome 7[3]. In these patients the clonal expansion, similar to what has been shown in acute myeloid leukemia (AML), usually arises in other subsets within the HPSC compartment.

The propensity for clonal instability and evolution is generally higher than in lower-risk MDS. Both low and high-risk MDS are considered incurable by conventional chemotherapy or other currently available therapies than allogeneic stem cell transplantation.

Standard risk assessment

Patients with MDS have an overall poor outcome, however, with a considerable variation between patient subgroups. The standard risk tool for patients with MDS is since 2012 the revised International Prognostic Scoring System (IPSS-R), dividing patients into 5 risk groups according to the degree of anemia, neutropenia, and thrombocytopenia, bone marrow blast percentage, and cytogenetic risk profile (Table 1)[6]. The IPSS-R has been validated in several publications, including its ability to guide decision-making for example with regard to SCT[7,8]. One important aspect is that a diagnosis of MDS always implies a decreased relative survival, i.e. a shorter life expectancy than for an age-and sex-matched person without MDS. In addition to the IPSS-R score, prognosis is influenced by the presence of grade 2 or 3 fibrosis which is independently associated with inferior outcome[9]. Moreover, comorbidities are also important, in particular when planning for more toxic treatment modalities. An MDS-specific index (MDS-CI) has been developed based on presence of: cardiac, liver, renal, or pulmonary disease, or presence of other tumors[10].

Table 1

Risk factor	0	+0.5	+1	+1.5	+2	+4	+5
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blasts, %	≤2%	-	2.1%-4.9%	-	5%-10%	>10%	-
Hemoglobin	≥100	-	80-99	<80			
Platelets	≥100	50-99	<50				
ANC	≥0.8	<0.8					

Risk group	Risk score	Patient distribution (%)	Median OS (years)	Median time to 25% AML evolution (years)
Very low	≤1.5	19	8.8	Not reached
Low	2-3	38	5.3	10.8
Intermediate	3.5-4.5	20	3.0	3.2
High	5-6	13	1.6	1.4
Very high	>6	10	0.8	0.7

Cytogenetic group

- Very good: *del(11q) or –Y*

- Good: *normal karyotype, del(20q), del(5q), del(12p), or double including del(5q)*

- Intermediate: *+8, del(7q), i(17q), +19, or any other single or double independent clone*

- Poor: *-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), or complex (3 abnormalities)*

- Very poor: *complex >3 abnormalities*

Molecular diagnostics and additional prognostic factors

Mutation screening has in recent years become readily available and more affordable. The presence of adverse mutations may support the clinical decision to transplant a low or intermediate risk patient with MDS, in particular in case of severe cytopenias. Both the type and number of mutations have prognostic implications[11-14]. Mutations associated with poor prognosis include: TP53, EZH2, ETV6, RUNX1, NRAS, and ASXL1. The only mutation consistently associated with favorable outcome is SF3B1, commonly observed in MDS-RS. AML-like mutations such as NPM1, NRAS, FLT3 are associated with transformed disease.

Aside from prognostic implications, mutational screening can be of value in borderline cases were a morphologic diagnosis of MDS is challenging; 80-90% of MDS patients carry at least one recurrent mutation[11,12]. However, a caveat is that the aging bone marrow is increasingly prone to harbor clonal hematopoiesis, without necessarily resulting in cytopenias or disease. The term CHIP (clonal hematopoiesis of indeterminate potential) is used for this condition, and it carries approximately a 1% annual risk of evolving to MDS[15].

Currently, a rational approach could be to genetically characterize transplant candidates as well as unexplained cytopenias that do not fulfill the criteria of MDS. (**Figura 1**)

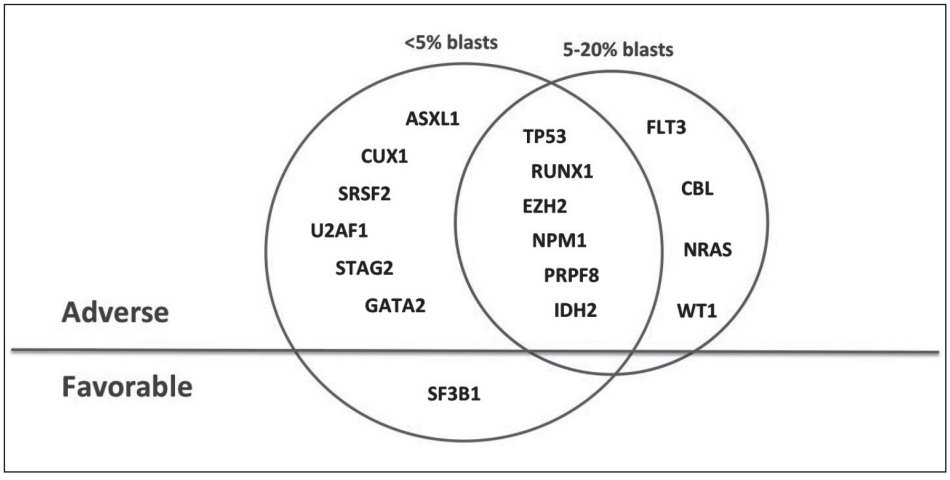

Figure 1. *Most mutations may occur at early phases of MDS and can cooperate to cause disease progression. A few mutations are tightly associated with blast increase, and only SF3B1 is linked to favorable outcome.*

Treatment of MDS

Patients with MDS are treated of two main reasons: To prolong survival and hopefully cure the disease, and to improve symptoms, thereby quality of life. Naturally these two purposes frequently overlap. In the Nordic guidelines for MDS, we have stressed the process that all newly diagnosed patients below the age of 75 years should undergo molecular risk profiling and be evaluated for a potential cure with stem cell transplantation. Still, a majority of these patients will probably not proceed to SCT, but we know for certain that transplantation after further clonal evolution and progression to overt high-risk MDS or acute leukemia is significantly associated with decreased outcome after transplantation.

Treatment with erythropoiesis-stimulating agents (ESAs)

Anemia is often the only significant cytopenia in lower-risk MDS. The anemia of MDS and chronic transfusion-dependency are according to most studies significantly associated with reduced quality of life and decreased survival[7,16]. When comparing patients with and without transfusion need but with the same IPSS-R score, transfusion dependency is significantly associated with both reduced survival and a higher risk for disease progression. The reason for the poorer outcome is probably multi-factorial and includes effects of chronic anemia on cardiovascular morbidity and chronic iron overload. It is also likely that transfusion need reflects more severe disease biology.

Erythropoietin (EPO) is first-line treatment for the anemia of lower-risk MDS, according to the European guidelines and should be offered to patients with symptomatic anemia[17]. The efficacy of EPO may be enhanced or restored by the addition of granulocyte-CSF (G-CSF), which acts synergistically with EPO to inhibit mitochondria-mediated erythroid apoptosis. Based on studies performed more than 20 years ago when patients usually were treated later in their disease, a transfusion need equal or above 2 red blood cell units per month and a serum erythropoietin ≥500 U/l predicted for a very poor response to treatment. This is still valid and ESAs should not be used in these patients, often characterized by marked erythroid hypoplasia in the bone marrow. However, as more treatment options emerge for patients with lower-risk MDS, better tools are needed to discriminate patients with poor and intermediate response probabilities, respectively. In a recent study, Buckstein and colleges describe 996 ESA-treated patients from three registries[18]. Overall response rate was 59%, which reflects the fact that patients today are treated earlier in their disease. By multivariate analysis, transfusion independence, erythropoietin (EPO) level <100 IU/L, and IPSS low-risk were independently predictive of response. Assigning a score of 1 to each resulted in a scoring system of 0-3 with response rates of 23%, 43%, 67%, and 85%. This new 'ITACA' score has a higher discriminating power of response than previously published scores.

ESA treatment has been associated with an improved survival in large retrospective studies mainly encompassing studies performed 1990 to 2000, using matched untreated patient cohorts as control[12,13,19,20]. The EU MDS Registry prospectively enrolls patients with lower-risk MDS treated within routine clinical practice at smaller and larger European hospitals. A recent study describes the outcome of 1696 patients in the registry, randomly treated with ESA or not based on local routines, reimbursement policy and other factors. Importantly, ESA treatment initiated in patients with Hb levels less than 10 g/dl but prior to a permanent transfusion need significantly delayed the onset of chronic transfusion dependency ($p<0.0001$). These recent large studies clearly shows that early ESA treatment is the preferred mode of treatment, which should be reflected in future guidelines and National reimbursement policies.

Immunosuppressive treatment in lower-risk MDS

A small fraction of low risk MDS patients with MDS-SLD and MDS-MLD seem to have bone marrow failure due to autoimmune mechanisms, as known from aplastic anemia[21]. Several international studies have demonstrated response rates in the order of 30% to immunosuppressive therapy (antithymocyte globulin [ATG] in some investigations combined with cyclosporin A [CyA]) in patients with MDS-SLD and MDS-MLD. HLA-DR15 positivity, young age and short duration of red cell transfusion dependence seem to predict for a response to immunosuppressive therapy in MDS patients, although this is based on a limited material. An analysis of patients treated at NIH indicated an improvement in survival of ATG treated patients, especially in younger individuals with lower risk disease. To date, there are no controlled data to support the addition of cyclosporin A to ATG treatment in MDS, although this combination has been shown to increase the response rate in a retrospective analysis.

Novel therapeutic options for MDS with ring sideroblasts

Luspatercept has emerged as a novel treatment for EPO resistant anemia in MDS with ring sideroblasts, as recently reported in a pivotal Phase I-II study showing IWG hematologic improvement of better in 63% of 51 patients treated with effective doses[22]. 42 patients were evaluable for transfusion independency and 16 of these (38%) achieved RBC-TI. Of the 22 patients who entered the extension phase study, 50% had a continued response with a median duration of 15 months. Treatment response was significantly associated with mutations in SF3B1, a core component of the spliceasome. Hence, novel therapeutic alternatives targeted to specific molecular alterations are part of the future for treatment of lower-risk MDS.

MDS del(5q) and lenalidomide

Lenalidomide binds to cereblon, a substrate adaptor of the $CRL4^{CRBN}$ E3 ubiquitin ligase, and modulates the ubiquination and degradation of specific proteins. One important target is CK1α, which is already haploinsufficient in MDS with del(5q), and its degradation leads to p53 dependent apoptosis in the MDS cells[23]. Lenalidomide is highly efficient in low risk MDS with del(5q), where 43-56% achieve transfusion-independency and 23-57%

show cytogenetic response[24,25]. The response rate is better with 10 mg/day 21/28 days compared to 5 mg continuous dosing, without added toxicity. Grade III-IV neutropenia and thrombocytopenia occurs in around 50% of patients, in particular early on during the treatment. The response duration is around 2 years.

The cumulative incidence of AML evolution in treated patients is around 35% at 5 years. Subclones with mutations in TP53 or RUNX1 are tightly linked to disease progression. The mutated clones may be small, down to 1%, and require deep sequencing to be detected. Immunohistochemistry demonstrating strong nuclear staining of p53 is tightly linked to mutation in TP53, and can be used as a surrogate marker[5,26,27]. Candidates for allogeneic stem cell transplantations should likely not be treated with lenalidomide; if treatment is given the patient should be carefully monitored for signs of progression. Patients with mutations in TP53 or RUNX1 should be evaluated for alternative treatments due to their adverse prognosis, and lenalidomide should only be considered were no suitable alternative is available.

Azacitidine

Due to the epigenetic effects of Aza and Dec, these drugs were termed hypomethylating agents. Two large randomized studies have evaluated the effects of Aza on MDS. The first study included all subtypes of MDS (n=99) and patients were randomized to receive either Aza or supportive care. Overall response rate was 60% in the Aza group, which was significantly better than the control arm ($p<0.001$). There was also a significant difference in progression-free survival (21 vs 12 months; $p=0.007$) but no significant difference in overall survival could be demonstrated (20 vs 14 months; $p=0.1$). The next study included only patients with higher-risk MDS (n=357) and randomized these into either Aza or best available treatment which consisted of intensive chemotherapy, low-dose cytarabine or supportive care. In this study a significant survival benefit could be demonstrated (24.5 vs 15 months; $p<0.001$). Both randomized studies show that responses are normally not seen before the patient has received ≥3 cycles and best response is often seen several cycles after the initial response. A post-hoc analysis of the European study showed a survival benefit also for patients with stable disease[28].

The effect of azacytidine in lower-risk MDS is less well studied and evidence from randomized studies for this treatment is lacking. Several phase-II studies in mostly transfusion-dependent patients, have demonstrated effect in lower-risk MDS although the response rate seems to be lower than in higher-risk patients and a positive effect on long-term outcome has hitherto not been demonstrated. A large randomized study (https://clinicaltrials.gov/ct2/show/NCT01566695) assessing the effect of oral Aza in lower-risk patients is ongoing and will hopefully bring more clarity into its role in lower-risk MDS.

Since the response is often delayed several months after start of treatment, predictive tools are highly warranted. Basic clinical data such as morphology and cytogenetics give sparse predictive information, although blast count > 15%, extensive transfusion requirements, abnormal karyotype and previous therapy with cytarabine have been reported as negative predictors of response[29-31]. Results from different studies regarding the effects of the mutational profile on response and survival after start of treatment are conflicting. Several studies report higher response rates for *TET2*–mutated patients but the presence of this mutation has not been associated with prolonged survival during treatment[31-33]. Another study demonstrated prolonged survival for patients having mutations in any of the histone modulating enzymes (ASXL1, EZH2)[34]. Survival benefit has also been demonstrated for patients with IDH1/2 mutations (Dec)[35]. One study reports high response rates of Dec in TP53-mutated patients with MDS and AML[36]. This is however in contrast to other studies on hypomethylating agents on TP53-patients where response and survival is rather reduced[34,37].

An initial reduction of methylation levels after the first treatment cycle in specific genes or on a global level was shown to predict a later clinical response[38-42]. If this is reflecting a causative or confounding effect of Aza is however not known. A few studies have reported correlation between methylation level of specific genes e.g. p15 and responses[43,44]. In contrast, other studies report no correlation between baseline methylation levels and response[40,45]. A recent study has shown that patients with hematopoietic progenitor cells in cell cycle have better response to Aza[46]. In summary, larger studies including basic clinical data, mutational and

epigenetic profile is needed to create a clinically useful predictive tool.

The pharmacodynamic effects of Aza are still quite enigmatic. The ruling paradigm for the mechanism of action of Aza claims that promotor demethylation results in re-expression of tumor suppressor genes silenced by aberrant DNA methylation[40]. There is however still a lack of convincing evidence confirming this paradigm. In addition to the demethylating effects, there is support for a direct cytotoxic effect, differentiation-promoting effect and direct effects on RNA[47-49]. Very interesting in vitro-studies have shown that Aza upregulates retrotransposons which evokes the innate immune system[50-52].

Other emerging treatments

Several promising therapies are being evaluated in MDS, including drugs targeting specific mutated proteins. Inhibitors of IDH1 and IDH2 are being explored in both MDS and AML, based on highly promising in vitro data. In relapsed/refractory AML, the IDH2 inihibitor enasidenib demonstrated a 40% over all response rate with 19% complete remissions, and the drug was approved for this indication by the FDA in August 2017[53]. Preliminary data suggests high efficacy also in MDS, and it will be important to assess whether this is dependent on the clone size or concurrent mutations.

Another target is BCL2, which is an anti-apoptotic protein that is upregulated in high risk MDS and in AML. Preliminary reports of the BCL2 inhibitor venetoclax have demonstrated high activity in MDS and AML both as a single drug and in combination with low-dose Ara-C or hypomethylating agents. In July 2017 it received a breakthrough status for AML by the FDA. Ongoing studies will demonstrate how lasting the responses are, and whether certain subgroups are more sensitive.

Novel hypomethylating agents including guadecitabine and oral azacytidine are being explored both as single drugs as well as in combination with other drugs such as the kinase inhibitor rigosertib. Moreover, early attempts are being made to identify druggable targets caused by alternative splicing, since splicing mutations are seen in around 50% of patients with MDS.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation (SCT) for patients with MDS has been performed since the 1970s, initially using sibling donors, but over time with a higher frequency of matched unrelated donors, cord blood or more recently also haploidentical donors. Since allogeneic stem cell transplantation (SCT) is the only potentially curative treatment in MDS, all patients should be evaluated for this option. However, due to the potentially severe complications, transplantation can only be performed in patients up to around 70-75 years of age without significant comorbidity. In younger patients a myeloablative conditioning is normally chosen, while older patients receive a reduced intensity conditioning, which reduces transplantation-related mortality but increases the risk of relapse. Long-term survival rates of between 25% and 45% have been reported after transplantation[54-56]. Transplantation-related mortality (TRM) and after myeloablative conditioning and reduced intensity conditioning has been reported to be 32% and 22% and relapse rate 22% vs. 45%, respectively[54]. Due to the high risk of TRM, timing of SCT is of great importance where higher-risk patients is recommended to proceed to SCT upfront while lower-risk patients should follow a strict surveillance program and be transplanted in case of signs of progression[57]. Recent possibilities to determine what genes are mutated using targeted panel sequencing, enables risk assessment for potential transplantation candidates with higher accuracy and patients with a more indolent disease, as predicted by the risk score, might still be transplantation candidates due to high-risk mutations, e.g. TP53 or RUNX1.

All three prognostic scoring systems (IPSS, IPSS-R and WPSS) have been validated to also predict survival after allogeneic stem cell transplantation[55,56,58,59]. The most important risk factor for relapse is genetics. Relapse-free survival at 5 years post transplantation in the five IPSS-R cytogenetic risk groups are reported to be 42%, 36%, 36%, 22% and 10%, respectively[55]. More recent data, based on the additional impact of mutations as assessed by targeted panel sequencing, report an increased risk of relapse for patients with mutations in TP53, TET2 or mutations involving RAS-pathway genes[60,61].

In addition to genetics, disease status has impact on survival and debulking treatment e.g. azacitidine or intensive chemotherapy is usually given for patient with a more proliferative disease aiming for the best possible remission prior to transplantation[17,56]. The

usefuless of debulking treatment has however never been tested in prospective controlled studies and there are retrospective studies indicating a similar outcome independent of debulking or not although selection bias is an obvious potential pitfall in these studies[62,63]. Likewise, retrospective studies have not been able to demonstrate any advantage for either hypomethylating therapy or intensive chemotherapy as debulking treatment[64,65].

The prognosis after a relapse is dismal although donor lymphocyte infusion might reverse the relapse in rare cases and azacitidine might prolong survival[66]. We and others have previously demonstrated that surveillance by using a chimerism analysis can be used to predict an impending relapse after SCT and serve as trigger for preemptive treatment, however, this analysis has low sensitivity and most often turns postive when the relapse is manifest and no longer possible to treat[67,68]. We are in the nordic MDS group now conducting a clinical trial where we evaluate a concept of determining the patient-specific mutations which are then followed by PCR after transplantation systematically in a prospective study (**Figure 2**). Preliminary data indicate that these markers can predict relapse which would enable preemptive treatment before the relapse has become manifest (https://clinicaltrials.gov/ct2/show/NCT02872662).

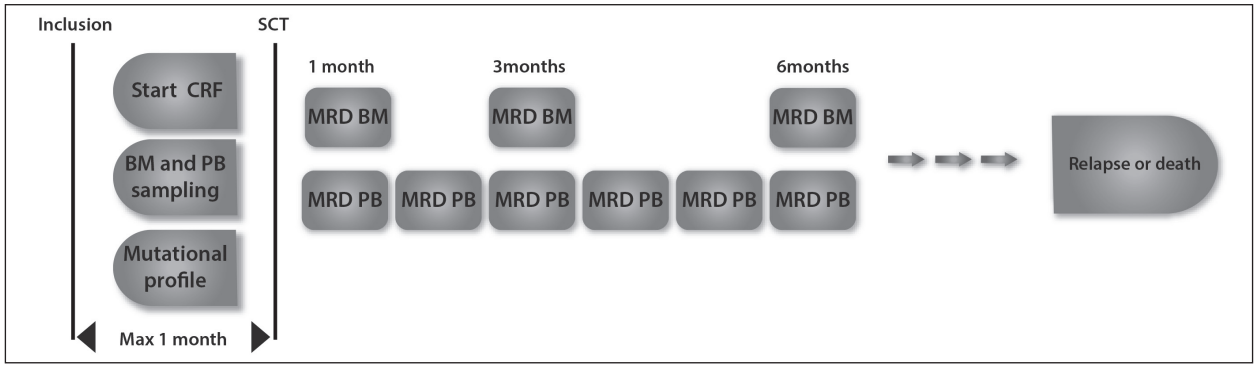

Figure 2. *Design of the prospective Nordic MDS group study 14B, evaluating patient-specific mutations, followed by PCR as MRD markers after transplantation.*

Declaración de conflictos de interés:
Martin Jädersten declara haber recibido honorarios por parte de Novartis en concepto de actividades educativas. El resto de los autores declara no poseer conflictos de interés.

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