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Retuning the immune system in myelodysplastic syndromes: from immunomodulatory approaches to vaccination strategies and non myeloablative hemopoietic cell transplant

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ABSTRACT

Several findings suggest that the pathogenesis and clinical history of myelodysplastic syndromes (MDS) is influenced by a variety of immune pathways and mechanisms. Coherently several therapeutic approaches based on the idea of modulating the immune system have been exploited in this clinical setting. The present review will first consider more consolidated strategies such as antithymocyte globulin and immunomodulatory (IMiDs) analogues. Less explored approaches, such as anti tumor necrosis factor antibodies, cyclosporin and bortezomib will be also evaluated. Finally the potential impact of anti-tumour vaccination or hemopoietic cell transplantation on the outcome of MDS patients will be addressed.

1. Introduction

The pathogenesis of myelodysplastic syndromes (MDS) is mainly driven by specific genetic lesions involving the stem cell compartment (Papaemmanuil et al., 2013). However clinical and laboratory findings suggest a potential role for different immune pathways and mechanisms (Fig. 1) (Fozza, 2017). In fact, a variety of autoimmune manifestations impact on the clinical history of around one third of MDS patients (Table 1). These conditions are extremely heterogeneous ranging from localized to systemic disorders and have been reported to potentially involve all sites and organs (Komrokji et al., 2016). Furthermore immunosuppressive treatments, starting with antithymocyte globulin (ATG), have been exploited in a fraction of these patients (Molldrem et al., 1997). Noteworthy, several immune cell subsets are deeply deranged and T-cells have been often advocated for the functional inhibition of hematopoietic precursors. The potential influence on the MDS pathogenesis of a large number of immune cell subsets has been specifically investigated by using different methodological approaches. Historically most studies were focused on cytotoxic T-cells and natural killer cells but more recently new characters, such as for instance regulatory T-cells and mesenchymal stem cells, have been widely evaluated in this clinical context. Relevant findings have been also reported as regards B cells, dendritic cells, macrophages as well as myeloid-derived suppressor cells (Fozza and Longinotti, 2012). The present review will first consider more consolidated strategies such as antithymocyte globulin and immunomodulatory (IMiDs) analogues. Less explored approaches, such as anti Tumor Necrosis Factor antibodies, cyclosporin and bortezomib will be also evaluated. Finally the potential impact of vaccination or stem cell transplantation on the outcome of MDS patients will be addressed (Table 2).

2. Antithymocyte globulin

After the first experiences dating back to 1988 (Tichelli et al., 1988), ten years later 25 transfusion-dependent patients were treated with ATG within a phase II study. Noteworthy, 44% of them responded and became transfusion-independent for a median of 10 months, while 3 of them even showed complete responses (Molldrem et al., 1997). A retrospective multicenter analysis focusing on 96 patients with MDS with a median follow-up of 33.8 months was reported. A total of 40 patients (42%) achieved an hematological response, 30 of which (75%) were durable lasting for a median of 31.5 months. On multivariate analysis, both low International Prognostic Scoring System (IPSS) and bone marrow hypocellularity were independent predictive factors for improved response to ATG while IPSS was the only predictor for overall survival (Lim et al., 2007). In a further prospective study among 61 patients, within 8 months of treatment 34% of them achieved red blood cell transfusion independence which was maintained in 81% of responders for a median of 36 months. Moreover 10 out of 21 patients (47.5%) with severe thrombocytopenia had sustained platelet count increases while 6 out of 11 patients (55%) with severe neutropenia had sustained neutrophil count increases (Molldrem et al., 2002). In a further phase II study 35 patients were treated with either horse or rabbit ATG with no differences in the observed response rates. Shorter disease history and belonging to the refractory anaemia (RA) subgroup correlated with response, whose median duration was 9 months. Noteworthy 23 patients experienced side effects > grade 2, with one patient dying from rhinocerebral mucormicosis (Stadler et al., 2004). In the context

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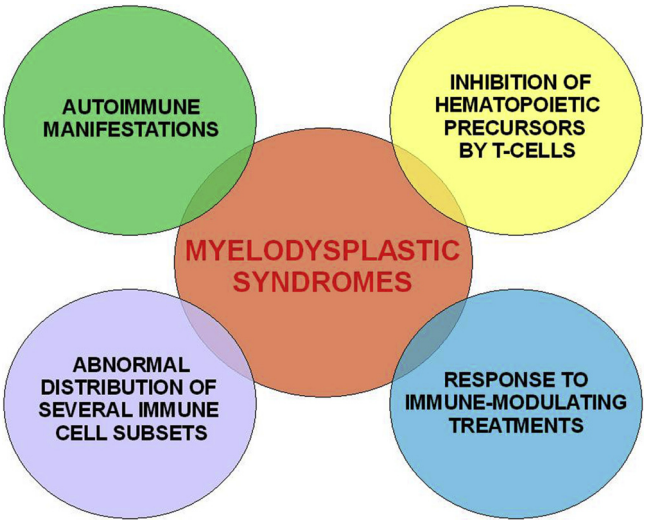

Fig. 1. The immune landscape of myelodysplastic syndromes.

Table 1
Most frequent autoimmune manifestations in MDS patients.

Haematological	**Gastrointestinal system**
autoimmune haemolytic anaemia	Behcet disease
immune thrombocytopenia	autoimmune pancreatitis
Vessels	autoimmune hepatitis
large-vessel vasculitis	**Kidneys**
Henoch Schönlein purpura	membranous gromerulonephritis
leukocytoclastic vasculitis	**Other organs and conditions**
Joints	systemic lupus erythematosus
relapsing polychondritis	Sjogren disease
rheumatoid arthritis	hypothyroidism
Skin	
neutrophilic dermatosis	
psoriasis	

Table 2
Immune-therapeutic approaches most often exploited in MDS patients.

antithymocyte globulin
thalidomide and its immunomodulatory (IMiDs) analogues
anti tumor necrosis factor antibodies
cyclosporin
bortezomib
sirolimus
temsirolimus
mycophenolate mofetil
alemtuzumab
vaccination strategy
non myeloablative stem cell transplant

of another phase II study T-cell activation profiling was proposed as a possible tool to predict the response to ATG (Komrokji et al., 2014).

After the first studies suggesting a potential role for the combination between ATG and cyclosporin in small cohorts of MDS patients (Yazji et al., 2003; Broliden et al., 2006; Garg et al., 2009), 15 mg/kg of horse ATG for 5 days and oral cyclosporin for 180 days were compared with best supportive care within a phase III trial. Although by month 6, 13 of 45 patients on ATG + cyclosporin had an hematologic response compared with only 4 of 43 patients on best supportive care, no apparent impact on transformation free and overall survival could be demonstrated (Passweg et al., 2011). In the context of a large retrospective study involving 66 patients all of which received ATG and 60% also cyclosporin, this association was shown to offer responses not inferior to other therapies approved for lower risk MDS. High risk revised International Prognostic Scoring System (IPSSR), poor karyotype and treatment after 2 years from diagnosis showed a negative impact on response rates. The association offered higher response rates than ATG alone while ATG administered in first line or after lenalidomide showed better response trend compared to when administered in third line or after azacytidine (Haider et al., 2016). Factors affecting response and survival in patients treated with ATG and/or cyclosporin were specifically evaluated in 129 patients. Thirty-nine (30%) of them responded either completely or partially: 18 (24%) of 74 patients to ATG only, 20 (48%) of 42 patients to ATG plus cyclosporin, and one (8%) of 13 patients to cyclosporin only. Thirty-one percent (12 of 39) of the responses were complete. In multivariate analysis, younger age was the most significant factor favouring response to therapy while other favourable factors were HLA-DR 15 positivity and combination of ATG plus cyclosporin (Sloand et al., 2008). Most studies evaluating ATG both in monotherapy and in combination confirmed that this drug is not devoid of toxicity, further highlighting the crucial relevance of a well balanced patient selection.

When looking at potential mechanisms of ATG efficacy, responses were associated with a loss of the lymphocyte-mediated inhibition of hematopoietic precursors. In fact in responders peripheral blood lymphocytes suppressed colony forming unit-granulocyte macrophage (CFU-GM) in an ATG reversible way. Moreover, depleting either CD3+ or CD8+ lymphocytes in the bone marrow increased CFU-GM only in responding patients, who also showed a shift of the T-cell receptor (TCR) beta variable (BV) profile from clonal to polyclonal. These findings suggested that cytotoxic T-cell clones mediate the suppression of CFU-GM and, after ATG treatment, are replaced by polyclonal non autoreactive T-cells (Molldrem et al., 1998). Another study examining by spectratyping the TCR repertoires of 12 MDS patients during ATG treatment demonstrated that patients recovering an effective hematopoiesis lost their skewed peaks, thus suggesting loss or reduction of overrepresented clonal T-cell populations. In contrast, patients who did not recover effective hematopoiesis showed persistently skewed repertoires 3 to 6 months after treatment (Kochenderfer et al., 2002). A significant association was shown between HLA DR15 expression and response to immunosuppression as well as occurrence of paroxysmal nocturnal hemoglobinuria. Very likely the DR15 typing could identify a subset of MDS paralleling the immune pathogenesis of aplastic anaemia and susceptible to immunosuppressive treatments. Such an association was potentially explained with either the efficient presentation of bone marrow stem cell-derived antigens by specific HLA molecules or by the correlation with cytokine profiles favouring a pro-inflammatory bone marrow microenvironment (Saunthararajah et al., 2002). It is worth reporting two different possible nuances of the ATG activity which, although deriving from in vitro studies applied to different contexts, fit quite well with the efficacy demonstrated in MDS. In fact ATG has been shown to induce the expansion of CD4+CD25+Foxp3+ regulatory T cells (Lopez et al., 2006), which are known to be abnormally distributed in MDS (Fozza et al., 2012), as well as to impair the interactions between T cells and antigen presenting cells (Haidinger et al., 2007). All these findings delineate the ideal MDS patient candidate to ATG and/or cyclosporin as younger, pancytopenic, hypoplastic, at lower risk and displaying normal karyotype beside HLA-DR15- positivity.

3. Thalidomide and its immunomodulatory (IMiDs) analogues

Thalidomide is known to act through several mechanisms of action including cytokine inhibition, modulation of cell adhesion to bone-marrow stromal cells, cytotoxic and anti-angiogenic effects. In the largest phase-II study evaluating single agent thalidomide in 83 patients with early and advanced MDS, 18% showed hematologic improvement, including 10 transfusion-dependent patients who became transfusion-independent (Raza et al., 2001). Other studies substantially confirmed these results, although the unfavourable safety profile usually limited long-term administration (Zorat et al., 2001; Bouscary et al., 2005). Noteworthy, several different possible combinations have been exploited with variable results, among which those including erythroid

stimulating agents (Kelaidi et al., 2008; Musto et al., 2006), arsenic trioxide (Raza et al., 2004a; Wei et al., 2012), azacytidine (Raza et al., 2008a; Kenealy et al., 2017), cyclosporin (Xiao et al., 2011) or topotecan (Raza et al., 2006).

Lenalidomide, which shares most of the immunological properties of Thalidomide, has initially showed its efficacy in a non selected MDS population (List et al., 2005). Since then a number of different studies have shown a specific efficacy in patients with 5q deletion especially in the low risk (Fenaux et al., 2011; Oliva et al., 2013; Sánchez-García et al., 2014; Giagounidis et al., 2014; Oliva et al., 2015; Schuler et al., 2016) but potentially also in the high risk setting (Adès et al., 2009; Chen et al., 2012). Major toxicity was represented by neutropenia and thrombocytopenia however in the context of an acceptable benefit/risk profile. Lenalidomide is known to induce ubiquitination and degradation of specific substrates, including casein kinase 1A1, a serine/threonine kinase encoded by a gene within the common deleted region for del5q. The degradation of this protein induces apoptosis via p53 activation. The haploinsufficent expression of CK1A1 in 5q- patients sensitizes cells to lenalidomide action, explaining its efficacy in this setting (Kronke et al., 2015). Interestingly lenalidomide has also shown a possible although less pronounced efficacy also in patients not carrying the 5q deletion (Raza et al., 2008b; Sibon et al., 2012; Santini et al., 2016), even if not all the studies confirmed this potential beneficial effect (Park et al., 2017). In particular an international phase III, randomized, placebo-controlled, double-blind study assessed the efficacy and safety of lenalidomide in transfusion-dependent patients with IPSS lower-risk non-del(5q) MDS ineligible for or refractory to erythropoiesis-stimulating agents. Among 239 patients transfusion independence was achieved in 26.9% of patients and its median duration was 30.9 weeks (Santini et al., 2016). Among the different potential combination, the simultaneous or sequential use of lenalidomide and azacytidine has shown the most promising results (Sekeres MA List et al., 2010; Sekeres et al., 2012; Platzbecker et al., 2013; DiNardo et al., 2015; Mittelman et al., 2016; Sekeres et al., 2017) while preliminary data suggest also a possible efficacy for the combination with bortezomib (Attar et al., 2013). However it should be underlined that until now the combination therapy between lenalidomide and azacytidine has not been demonstrated to be superior to azacitidine monotherapy in terms of overall response rate and survival, mainly for greater toxicity requiring more often dose modification and early treatment discontinuation. More recently higher doses of lenalidomide have been tested in patients with relapsed or refractory high risk MDS and acute myeloid leukemia (AML) with discouraging results (Zeidan et al., 2017). A recent meta-analysis has conclusively confirmed an increased overall survival as well as a reduced rate of progression into AML for patients with 5q deletion (Lian et al., 2016). The immunomodulatory activity of lenalidomide in low-risk MDS patients is at least partially related to its effects on T-cell activity, including reduction in T-cell tolerance, increased effector function and establishment of a normal T-cell homeostasis. In fact, although the in vitro inducible T-cell proliferation was reduced in MDS patients for both CD4+ and CD8+ cells, TCR stimulation in the presence of lenalidomide induced significantly greater proliferation in both cell subsets, beside an increased production of Th1-type cytokines which are effectors of anti-tumor immunity. In vivo, a significant improvement in the ratio of naïve-to-memory T-cells was seen in MDS patients with erythropoietic response to lenalidomide, suggesting that lenalidomide increases proliferation and/or thymic output, therefore improving the homeostasis within the T-cell compartment (Mc Daniel et al., 2012).

4. Anti tumor necrosis factor antibodies

After the first attempts in 2002 showing quite conflicting results (Maciejewski et al., 2002; Deeg et al., 2002; Rosenfeld and Bedell, 2002), Infliximab, an anti tumor necrosis factor (TNF)-alpha chimeric monoclonal antibody, was tested in 37 patients with low risk disease, 22% of which showed an hematologic response with a good safety profile (Raza et al., 2004b). Very interestingly, also SCIO-469, a p38 a-mitogen-activated protein kinase inhibitor, which is able to suppress the induction of TNF-alpha, vascular endothelial growth factor (VEGF), IL-6, and IL-1b and is usually applied to rheumatologic disorders, has preliminary shown potential activity in restoring hematopoiesis in MDS progenitors (Navas et al., 2006). The administration of the anti-TNF-alpha monoclonal antibody cA2 reduced the proportion of apoptotic and Fas + cells in the CD34+ cell compartment and increased the clonogenic potential of bone marrow mononuclear and CD34+ cells. Moreover in long-term bone marrow cultures the antibody reduced TNF-alpha levels and significantly improved the hematopoiesis-supporting capacity of adherent cells. Finally the proportion of activated peripheral blood and bone marrow T lymphocytes decreased significantly after treatment, therefore suggesting an immunomodulatory effect of cA2 (Boula et al., 2006). All these preliminary findings should be further exploited in the context of clinical studies.

5. Cyclosporin

Haematological responses in terms of anaemia improvement and achievement of transfusion independence were also observed in 82% of cytopenic patients with RA treated with cyclosporin A. A complete trilineage recovery was observed in 23% of patients. Noteworthy responses were long-lasting with follow-up ranging from 5 to 30 months and this treatment was overall well tolerated (Jonásova et al., 1998). Interesting results were also reported in a small cohort of patients with erythroid hypoplasia (Shimamoto et al., 2001). In vitro studies demonstrated that, in patients with hypoplastic MDS, the addition of cyclosporin A to patients lymphocytes significantly decreased the number of IFN-gamma-expressing CD4+ cells. This effect was associated with increased colony formation, giving a possible explanation for the beneficial effect of this agent in this subset of patients (Selleri et al., 2002). Among 50 patients treated with a median dose of 4.58 mg/kg, hematological improvement was observed in 30 (60%) of patients all of them with RA while 4 (8%) of the responders achieved partial remission (PR) once again with a good safety profile. Higher response rate (53%) was shown in the erythroid compared to platelet or neutrophil lineage. Responses were associated with good karyotype or DRB1*1501 subtype (Shimamoto et al., 2003). A literature review confirmed that cyclosporin A therapy is useful for MDS patients with any marrow cellularity and that shorter disease duration and higher cyclosporin A dose are positively correlated with response rates (Ogata et al., 2004). The potential efficacy of such an approach was further confirmed in following studies, showing similar results (Dixit et al., 2005; Chen et al., 2007; Ishikawa et al., 2007). The importance of patient selection, in order to increase response rates and avoid treatment-related AML transformation, has been highlighted in a following trial, in which the response rate to ATG followed by cyclosporin A or cyclosporin A alone appeared to be positively correlated with the number of recruitment criteria met, i.e. IPSS ≤ 1 and at least one of the following criteria: expression of the HLA-DR15 allele, bone marrow cellularity of less than 30%, abnormal immune index of bone marrow T-lymphocytes. The overall response rate was 775%, with only 2 of 71 patients experiencing disease progression (Xiao et al., 2012). In a retrospective analysis among 89 low risk MDS patients treated with cyclosporin A and levamisole, 63 (708%) achieved either complete remission or hematological improvement at 4 months, with an estimate 24 month progression free survival (PFS) of 822% (Li et al., 2015).

6. Bortezomib

Although the proteasome inhibitor bortezomib is widely used in different onco-haematologic disorders, its mechanisms of action have been only partially clarified. A potential interest for its use in MDS patients relies on the demonstration that its efficacy is dependent on the

autophagy-mediated lysosomal degradation of the TNF receptor associated factor 6 (TRAF-6) (Fang et al., 2012). Two different studies have shown only a modest activity when administered in monotherapy in both a mixed cohort of MDS subjects (Alimena et al., 2011) or specifically in low-risk patients (Daher et al., 2017). Much better results were demonstrated among 43 higher risk patients. Interestingly responses were seen in 12 of the 43 patients (28%), including 1 complete response, 3 marrow complete responses, 5 partial responses and 3 haematological improvements. These responses were observed in 12 (36%) of the 33 previously untreated patients, compared to none in the 12 previously treated patients. Noteworthy responders showed improved overall survival. Main toxicity was haematological, responsible for infection in 6 patients and bleeding in 3. Three patients with grade 1–2 pre-treatment haematological toxicity developed grade 3–4 toxicity while neuropathy was seen in 12% of patients (Natarajan-Amé et al., 2012).

7. Other immunomodulatory approaches

Among 19 patients receiving sirolimus orally for a median of 3.7 months, 3 showed either a major or a minor haematological response according to International Working Group criteria (Platzbecker et al., 2005). On the other side temsirolimus at a dose of 25 mg per week was accompanied by considerable toxicity without beneficial effects in elderly MDS patients (Wermke et al., 2016). Interestingly transfusion independence was also achieved in 3 out 9 low risk MDS patients treated with mycophenolate mofetil (Remacha et al., 2010). Also the tumor growth factor (TGF)-beta receptor I kinase (Zhou et al., 2008) as well as IRAK1, an immune-modulating kinase (Rhyasen et al., 2013), were identified as potential therapeutic targets within in vitro studies.

Noteworthy also the programmed death 1 (PD-1) signaling was shown to be potentially involved in MDS pathogenesis and more importantly to resistance mechanisms to hypomethylating agents, thus suggesting its possible therapeutic targeting in order to overcome such a resistance (Yang et al., 2014; Ørskov et al., 2015).

A non randomized pilot phase I/II study with alemtuzumab monotherapy was performed in 32 patients with MDS who were judged likely to respond to immunosuppressive therapy. Seventeen (77%) out of 22 intermediate-1 and 4 (57%) out of 7 intermediate-2 patients responded with a median time to response of 3 months. Four out of 7 responders with cytogenetic abnormalities had normal cytogenetics by 1 year after treatment. Moreover among 9 responding patients evaluable at 12 months 5 (56%) had normal blood counts and 7 (78%) were transfusion independent. Thirteen patients were hospitalized for infections which were always self-limited. Lymphocyte depletion was universal by 24 h after initiation of infusion, and patients remained lymphopenic for up to 2 years after treatment (Sloand et al., 2010).

Interestingly also the IL8-CXCR2 pathway (Schinke et al., 2015) and p38 MAPK and Tie2 kinases (Bachegowda et al., 2016) were advocated as potential targets, thus opening for ARRY614 -a specific inhibitor of the latter- potential therapeutic avenues (Garcia-Manero et al., 2015).

A single study specifically evaluated the potential efficacy of methylprednisolone with or without cyclosporin A in MDS subjects with less than 5% blast in peripheral blood, less than 10% blast in bone marrow and advanced cytopenia. Among 18 eligible patients 6 responded to immunosuppressive therapy, with no apparent impact from cyclsporin A. In

responders, mean hemoglobin levels were significantly increased and the required red cell transfusion dose was significantly reduced. The duration of response ranged from 4 to 59 months with a median of 14 months. Interestingly a significant difference in the survival rate was observed between responders and non responders (Yamada et al., 2003).

8. Vaccination strategy

Whereas many more data have been obtained in AML patients, the immunogenicity of Wilms tumor gene product 1 (WT1)-peptide vaccination was evaluated in a cohort of WT1-expressing patients including also 2 refractory with excess of blasts (RAEB). Both treated patients showed a major neutrophil response lasting for 2 and 10 months, detectable within 4 weeks of treatment and continuing until disease progression. In addition, one of them had a platelet response lasting for 3 months. These clinical results were paralleled by a decrease in WT1 m-RNA levels and by an increase of WT1-tetramer T-cells in both peripheral blood and bone marrow of most patients (Keilholz et al., 2009). The biological background of this promising strategy was further clarified by a following study showing that anti-WT1 CD4+ and CD8+ T-cell immune responses can be detected in MDS patients responsive to immunosuppressive therapy. Noteworthy, WT1-specific CD8+ T-cells consisted in oligoclonal lymphocyte expansions and were able to inhibit autologous bone marrow cells in culture (Sloand et al., 2011). More recently one of two patients with high-risk MDS vaccinated with a mixture of peptides derived from the WT1 protein experienced a prolonged decrease in transfusion dependence (Brayer et al., 2015). In a small cohort of MDS patients also high-dose RHAMM-R3 peptide vaccination was shown to induce specific immunological responses and positive clinical effects in terms of reduction of leukemic blasts or improvement of peripheral blood counts (Greiner et al., 2010). Finally PR1, an HLA-A2-restricted peptide derived from both proteinase 3 and neutrophil elastase, recognized on myeloid leukemia cells by cytotoxic T lymphocytes, has been evaluated within a phase I/II trial showing objective clinical responses paralleled by PR1-specific immune response also in some MDS patients (Qazilbash et al., 2017).

9. Non myeloablative hemopoietic cell transplant

Even if most of the efficacy of hemopoietic cell transplantation (HCT) is guaranteed by the anti-neoplastic activity exerted by both the conditioning regimen and donor lymphocytes within the so called graft versus leukaemia effect, we may still hypothesize a room for its immune modulatory properties especially in the context of reduced-intensity conditioning (RIC) transplant programs. Although also in MDS myeloablative and non myeloablative HCT approaches have substantially shown comparable results, most studies are based on mixed cohorts including also AML patients (de Witte et al., 2009; Alyea et al., 2006; Martino et al., 2006). More recently, even if based on a small number of subjects, a survival benefit was suggested for young lower-risk MDS patients without significant comorbidities undergoing a RIC transplant (Lee et al., 2011).

Focusing on more homogeneous and larger cohorts, the outcome of RIC allogeneic HCT was retrospectively evaluated in 43 patients with MDS or AML arising from MDS. All patients engrafted with a median neutrophil recovery of 15 days while the 2-year OS, disease-free survival (DFS), relapse and transplant-related mortality were 53%, 51%, 16% and 35%, respectively. Grade II−IV acute graft-versus-host disease (GVHD) occurred in 63% of patients. There was no significant survival difference between sibling and matched unrelated donor (MUD) HCT whereas the relapse rate was higher among sibling donor recipients when compared to MUD (38 versus 7%) (Nakamura et al., 2007). A following study analysed 128 consecutive patients who received RIC-HCT, 40 of which received azacytidine before transplant. With a median follow-up of 60 months, 3-year OS, relapse-free survival (RFS), cumulative incidence of relapse and non relapse mortality were, respectively, 53% versus 53%, 37% versus 42%, 35% versus 36% and 20% versus 23%, for patients receiving azacytidine or not. Multivariate analysis confirmed the absence of statistical differences in outcome between the two groups of patients (Damaj et al., 2014).

Very recently a busulfan-based RIC was compared with a myeloablative conditioning regimen (MAC) within a prospective, multicenter,

open-label, randomized phase III trial from the European Society of Blood and Marrow Transplantation in 129 patients with MDS or secondary AML. Once again no differences could be shown for engraftment, incidence of acute or chronic GVHD, non relapse mortality, relapse rate at 2 years, relapse-free survival and overall survival (Kröger et al., 2017). Notwithstanding the heterogeneous results obtained in MDS patients it is mandatory to keep in mind the HCT is still the only curative approach available for these patients.

10. Response of autoimmune manifestations to therapies for MDS

The biological interplay existing between the MDS pathogenesis and the development of autoimmune manifestations is mirrored by studies demonstrating the improvement or resolution of the latter after MDS modifying therapeutic approaches, among which more often 5-azacytidine and HCT.

In the largest available study the efficacy of azacytidine on autoimmune disorders was retrospectively assessed in 22 patients with MDS or chronic myelomonocytic leukaemia (CMML). Responses of autoimmune disorders were observed in 19 patients (86%) and reduction or discontinuation of steroids and/or immunosuppressive therapy was possible in 16 cases (73%). The evolution of MDS/CMML and autoimmune disorders was concordant in 13 cases (59%): both favourable in 11 cases and both unfavourable in 2. Noteworthy all responses of autoimmune disorders to azacytidine were observed by the third cycle, although about one third of responses improved and became complete between 3 and 6 cycles. Furthermore, although less than 50% of the patients received more than 6 cycles, only 3 relapses were observed (Fraison et al., 2016). In a different study in 11 patients treated with azacytidine, responses of their autoimmune disorders were achieved in 9/11 (80%) and 6/11 (55%) patients at 3 and 6 months, respectively (Mekinian et al., 2016). Noteworthy we have previously demonstrated that most of the T-cell abnormalities observed in MDS patients (Fozza et al., 2009) tend to revert during therapy with azacytidine, especially within the CD4+ subset (Fozza et al., 2015).

Also allogeneic HCT has been able to restore autoimmune disorders in some patients with MDS. The condition most often reported in this field was BD, which was resolved after cord blood HCT in 3 patients (Yamato, 2003; Tomonari et al., 2004; Nonami et al., 2007) and after peripheral blood HCT in one patient (Kook et al., 2014). Interestingly also relapsing polychondritis (Tomomatsu et al., 2012), Takayasu arteritis (Kato et al., 2014) and spondyloarthritis (Simonetta et al., 2015) were reported to respond to non myeloablative, cord blood and fully myeloablative HCT, respectively.

When considering a specular point of view, haematologic improvements have been described in some MDS patients receiving immunosuppressive treatments for their autoimmune manifestations. This scenario was assessed systematically in 30 patients with autoimmune disorders associated with MDS, among which most frequent were skin vasculitis and arthritis. Autoimmune manifestations responded to immunosuppressive therapy (primarily prednisone) in 26/27 patients. Quite strikingly, cytopenias improved substantially in 6 patients, including complete normalization of peripheral blood counts in two patients with cytogenetic remission in one. Patients with an haematological response to immunosuppressive therapy had improved survival. The autoimmune syndrome was implicated as a primary cause of death in 8/17 patients who died (Enright et al., 1995).

11. Recent systematic studies and conclusions

Although the pathogenesis of MDS is unequivocally driven by a milieu of molecular mechanisms, over the last few years a large number of studies have highlighted the potential role of specific immune pathways in this context (Fozza et al., 2016; Fozza and Longinotti, 2013). Concomitantly different groups have explored the possible effects of immune-modulating therapeutic approaches. After reporting several anecdotal cases, these findings have been progressively categorized within more systematic data collection or even clinical studies.

An interesting point of view was quite recently offered by a French multicenter retrospective study assessing the efficacy and safety of different biologics such as TNF-α antagonists, tocilizumab, rituximab and anakinra for systemic inflammatory and autoimmune diseases associated with MDS. Interestingly when several lines of treatment were used, data were analyzed before and at the end of each treatment line and were pooled to compare overall responses. Twenty-nine patients were included and the most common associated disorders were arthritis, relapsing polychondritis and vasculitis. During a 3-year median follow-up a total of 114 lines of treatments were used for all patients: steroids alone (22%), disease-modifying antirheumatic drugs (23%), TNF-α antagonists (14%), anakinra (10%), rituximab (10%), tocilizumab (7%) and azacytidine (9%). Considering all 114 lines, overall response was showed in 54% cases and was more frequent with steroids (78%) and rituximab (66%) than disease-modifying antirheumatic drugs (45%) and other biologics (33%). Rituximab offered better response in vasculitis and TNF-α antagonists in arthritis. During follow-up, 20 patients (71%) presented at least one severe infection (Mekinian et al., 2017).

From a different point of view, the clinical outcomes and predictors of response in patients with MDS treated with immunosuppressive therapies were studied in a large multi-center international cohort including 367 patients from 11 centers in the United States and in Europe. A total of 367 patients received immunosuppressive therapies, whose disease risk according to the IPSS was low (23%), int-1 (68%), or either int-2 or high (9%). The 149 (40.6%) patients in which only prednisone was used were excluded from response and survival analysis. Of the other 198 patients, immunosuppressive therapies used from most to least frequently was ATG (46%), cyclosporin (11%), tacrolimus (5%) and others (8%). ATG was combined with cyclosporin in 25% of patients. One hundred and fourteen of these 198 patients had response criteria reported: 13.2% had a complete remission, 5.3% had a partial response and 31.6% achieved hematologic improvement resulting in an overall response rate of 45%. In contrast, 38.6% of patients had stable disease (SD) and 11.4% had progressive disease (PD). Transfusion independence was achieved in 38.3% of patients. For patients who achieved a response to immunosuppressive therapies or transfusion independence a significant increase in overall survival was demonstrated. In univariate analyses, female sex predicted better overall survival whereas higher-risk IPSS and IPSS-R score predicted worse overall survival. In multivariate analyses, only bone marrow blast > 5% remained a statistically significant predictor of overall survival and no predictive factors for response were identified. Importantly and in comparison to prior reports, age, prior transfusion dependence, MDS risk scores, type of immunosuppressive therapies used, presence of a paroxysmal nocturnal hemoglobinuria or large granular lymphocyte clone and HLA DR15 positivity and mutations were not predictive of response (Stahl et al., 2017).

In conclusion, when considering that a good fraction of subjects with MDS is still candidate to therapeutic approaches which are able to modify only marginally the disease history as well as the unequivocal role of immune mechanisms in the pathogenesis of these disorders, we suggest that a strategy based on the idea of retuning the immune system would deserve to be further exploited in this clinical setting.

Conflicts of interest

Nothing to declare

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