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The Yin and Yang of myelodysplastic syndromes and autoimmunity: The paradox of autoimmune disorders responding to therapies specific for MDS

Claudio Fozza[a,*], Giorgio La Nasa[b], Giovanni Caocci[b]

[a] Hematology Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Viale San Pietro 12, 07100 Sassari, Italy
[b] Hematology Unit, Department of Medical Sciences, University of Cagliari, Cagliari, Italy

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ABSTRACT

The biological *milieu* and clinical picture of myelodysplastic syndromes (MDS) is characterised by a variety of immune mechanisms and manifestations, including an increased frequency of autoimmune disorders. The present review will try to shed some light on the potential clinical and pathogenetic implications of these immune processes in MDS by focusing on the beneficial effects exerted by some MDS-modifying therapies on autoimmune manifestations.

1. Introduction

In Taoism yin and yang describes how in the natural world seemingly opposite or contrary forces may actually be complementary and interdependent and how they may potentially give rise to each other. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematologic diseases, the pathogenesis of which is driven by specific molecular lesions involving the stem cell compartment (Papaemmanuil et al., 2013). However several findings suggest that the immune system of MDS patients is widely deranged and potentially involved in modulating disease evolution (Fig. 1) (Fozza et al., 2016). In fact, autoimmune disorders (AD) are reported in around one third of MDS patients (Komrokji et al., 2016; Fozza, 2018a) and the debate is still open about their potential prognostic implications (Fozza, 2018b). Moreover a fraction of MDS patients are known to respond to immunosuppressive treatments such as for instance antithymocyte globulin (Molldrem et al., 1997). Several immune cell subsets display anomalies in MDS patients (Fozza et al., 2016, 2012a; Fozza et al., 2012b) and in particular cytotoxic T-cells have been advocated in the functional inhibition of hematopoietic precursors (Smith and Smith, 1991; Fozza and Longinotti, 2013). All these data, along with the evidence that AD may respond to some MDS-modifying therapeutic approaches, potentially suggest that MDS and AD represent medical conditions which, like yin and yang, are deeply interconnected and can reciprocally influence each other (Fig. 2).

2. Autoimmune manifestations in patients with myelodysplastic syndromes

As already mentioned, around one third of MDS patients suffer form a variety of AD (Komrokji et al., 2016). The most frequent scenarios are autoimmune haemolytic anaemia (AHA) and vasculitis but the potential involvement of several different sites and organs has been described including skin, joints, gastrointestinal system and kidneys (Fozza, 2018a), as shown in Table 1. Apart form some anecdotal reports, such a clinical association has been more systematically addressed within registry studies, some of which were focalized on the potential impact of AD on the MDS kinetic, as shown in Table 2, while others evaluated the reciprocal risk existing between MDS and autoimmunity.

2.1. Prognostic implications of autoimmunity in MDS patients

Within the former some studies suggested a potential negative prognostic impact for AD in MDS patients. Among 153 patients, 19 of which experienced AD, there was no significant difference in the distribution of age, MDS subtype or sex between patients with and without immune clinical or laboratory abnormalities. However the survival of subjects with immune abnormalities was significantly worse due to both infection and leukemic progression (Okamoto et al., 1997). Among 117 MDS patients in which the most frequent autoimmune manifestations were rheumatoid arthritis and ulcerative colitis, subjects experiencing AD had a shorter median overall survival (OS) although leukemic transformation was not increased (Zhao et al., 2002). A possible

* Corresponding author at: Hematology Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Viale San Pietro 12, 07100, Sassari, Italy.
E-mail address: cfozza@uniss.it (C. Fozza).

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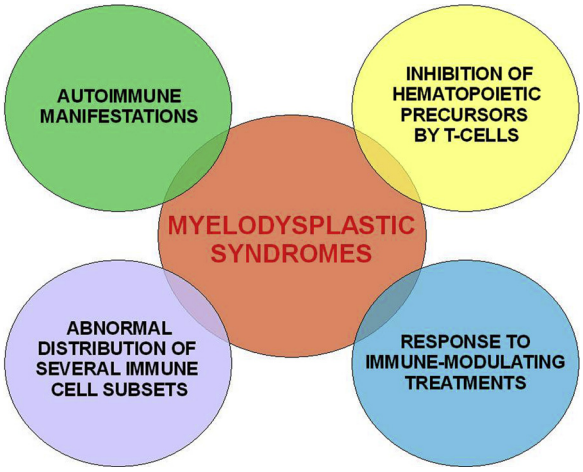

Fig. 1. The immune landscape of myelodysplastic syndromes.

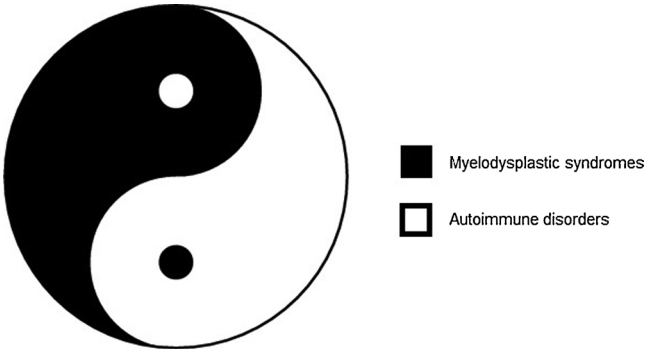

Fig. 2. Several clinical and laboratory findings suggest that myelodysplastic syndromes and autoimmune disorders represent medical conditions which, like yin and yang, are deeply interconnected and can reciprocally influence each other.

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	

negative prognostic impact was suggested by a further study, above all in patients suffering from vasculitis and/or cryoglobulins (de Hollanda et al., 2011). A following report based on 67 MDS patients with AD suggested that certain clinical pictures were associated with distinctive karyotypes and worse survival. Neutrophilic dermatosis and vasculitis usually appeared at the time of diagnosis whereas other manifestations occurred years after MDS diagnosis. Deletion of 5q was associated with neutrophilic dermatosis whereas trisomy 8 with Behçet disease (BD). Neutrophilic dermatosis was also associated with a 1.8-fold increase in mortality (Lee et al., 2016). In a series of 142 patients diagnosed with MDS and chronic myelomonocytic leukaemia (CMML) 48% of patients were diagnosed as having AD, being hypothyroidism the most commonly reported clinical manifestation (8%) and antinuclear antibodies

Table 2
Most relevant registry studies evaluating frequency and impact of autoimmune manifestations in MDS patients.

Authors, year of publication	Patients	Patients with autoimmune manifestations	Type of study	Main results	Impact on survival
(Okamoto et al., 1997)	153	19 (12%)	retrospective	survival of subjects with immune abnormalities significantly worse due to infections or leukemic progression	negative
(Zhao et al., 2002)	117	19 (16%)	retrospective	leukaemic transformation not increased but shorter median survival in subjects with autoimmune disorders	negative
(de Hollanda et al., 2011)	235	46 (20%)	retrospective	possible negative prognostic impact especially in patients with vasculitis and/or cryoglobulins	negative
(Lee et al., 2016)	201	67 (33%)	retrospective randomized	neutrophilic dermatosis associated with a 1.8-fold increase in mortality	negative
(Montoro et al., 2018)	142	68 (48%)	retrospective	autoimmune disorders (clinical but not isolated immune serological parameters) associated with inferior overall survival	negative
(Giannouli et al., 2004)	70	13 (19%)	prospective	no impact on disease characteristics and survival; in most patients autoimmune manifestations develop during the course of MDS	absent
(Marisavljević et al., 2006)	284	32 (11%)	retrospective	except for female predominance, no correlations between immune abnormalities and disease features or survival	absent
(Mekinian et al., 2016)	788	123 (16%)	retrospective	patients with autoimmune diseases were younger, male, less often with refractory anaemia with ring sideroblasts or low and intermediate-1 IPSS and more often with poor karyotype; no survival difference	absent
(Komrokji et al., 2016)	1408	391 (28%)	retrospective	by multivariate analysis autoimmune diseases were a positive independent factor for overall survival; rate of transformation into AML was decreased in patients with autoimmune disease	positive
(Seguier et al., 2019)	801	88 (11%)	retrospective	overall survival was better in patients with autoimmune disorders; such a positive impact was confined to patients with low or intermediate-1 IPSS and in which autoimmune disorders appeared concomitantly or after MDS	positive

the most frequently identified serological parameter (23.2%). The presence of AD was associated with female gender, lower hemoglobin levels, and higher revised international prognostic scoring system (IPSS-R) and much more importantly with inferior OS (69 vs. 88% at 30 months). Notably, such a negative prognostic impact was associated with clinical but not isolated immune serological parameters (Montoro et al., 2018).

On the other hand some studies did not suggest a correlation between MDS prognosis and occurrence of AD. Among 70 prospectively enrolled patients, 13 of which experienced autoimmune complications, no differences were detected concerning bone marrow blast count, international prognostic scoring system (IPSS), favourable cytogenetic abnormalities, leukaemic transformation and survival. Noteworthy the onset of AD preceded the diagnosis of MDS in a minority of patients, while in most of them they developed during the course of MDS (Giannouli et al., 2004). Similar results were suggested by a following study (Marisavljević et al., 2006). Within a study overall including 788 patients, interestingly 127 patients with MDS or CMML with systemic inflammatory disorders and AD were compared with 665 patients without these manifestations. The former were younger, male, less often had refractory anaemia with ring sideroblasts (RARS), more often had a poor karyotype and less frequently belonged to low and intermediate-1 IPSS categories, but no survival differences could be demonstrated (Mekinian et al., 2016). In a different cohort immune-mediated complications were shown to preferentially develop in patients with secondary MDS, in younger subjects and in patients with cytogenetic abnormalities (Billström et al., 1995). Our knowledge about the prognostic implications of autoimmune manifestations in MDS was markedly improved by the largest ever reported analysis performed on 1408 patients in the context of a joint effort from the Moffitt Cancer Center in Tampa and King's College Hospital in London. Twenty-eight percent of the patients had AD with hypothyroidism, idiopathic thrombocytopenic purpura, rheumatoid arthritis and psoriasis being the most common subtypes and accounting for 44%, 12%, 10% and 7% of patients respectively. AD were more common in female patients, in those with refractory anaemia (RA) or refractory cytopenia with multilineage dysplasia (RCMD) and in subjects less dependent on red blood cell transfusion. Quite strikingly median OS was 60 months for patients with AD versus 45 months for those without and by multivariate analysis AD were a statistically significant independent factor for OS. Moreover the rate of transformation into AML was 23% in patients with AD versus 30% in those without (Komrokji et al., 2016). A monocentric retrospective study evaluated 801 patients with MDS patients, 11% of which presented with AD. The most frequent manifestations were polyarthritis and autoimmune cytopenias. In the case control study WHO classification, karyotype abnormalities, IPSS-R and IPSS were similar in both groups. Noteworthy OS from MDS diagnosis was better in patients with AD (10.3 ± 0.6 versus 4.8 ± 1.1 years) and such a positive impact was confined to patients with low or intermediate-1 IPSS. The better survival was observed only when AD appeared concomitantly or after MDS and also steroid dependence was associated with a better survival (Seguier et al., 2019). We may hypothesize that the heterogeneous interpretation of the prognostic implications of AD in MDS patients could be at least partially ascribable to the different criteria adopted to classify AD. In fact, some clinical immune-mediated conditions, such as for instance thyroid disorders, were included in some studies but not in others and serological abnormalities were considered only within a minority of the reported analyses. However it is worth mentioning that all the largest reported studies suggested either a positive prognostic effect or a lack of impact.

2.2. Risk of developing MDS in patients with autoimmunity

Moving to projects exploring the reciprocal risk between MDS and autoimmunity, a registry study focusing on the risk of developing myeloid malignancies in patients with different AD, reported an increased risk for MDS, particularly high in AHA and polyarteritis nodosa (Anderson et al., 2009).

Within a large population-based central central registries in Sweden, including 9219 patients with AML, 1662 patients with MDS and 42,878 matched controls, chronic immune stimulation was further advocated as a possible trigger for the development of both AML and MDS. In fact, overall a history of any infectious disease was associated with a significantly increased risk of both AML (odds ratio -OR- 1.3) and MDS (OR 1.3). These associations were significant even when focusing on infections occurring 3 or more years before AML/MDS. A previous history of any AD was associated with a 1.7-fold increased risk for AML and 2.1-fold increased risk for MDS (Kristinsson et al., 2011). In a following study a slightly increased risk of MDS in patients with any AD was demonstrated and it was confined to patients diagnosed over 10 years prior to the index date and involved both untreated and heavily treated patients (Wilson et al., 2014).The association of cytotoxic, anti-inflammatory, and immunomodulating agents to treat patients with AD with the risk for developing myeloid neoplasm was specifically addressed within a retrospective case-control study including 86 patients who developed MDS or AML. Among them rheumatoid arthritis, psoriasis and systemic lupus erythematosus (SLE) were the most common autoimmune profiles. Median time from onset to diagnosis of myeloid neoplasm was 8 years. A total of 57 out of 86 cases (66.3%) received a cytotoxic or an immunomodulating agent. Azathioprine sodium use was observed more frequently in cases, with a 7-fold risk for myeloid neoplasm. No significant association between a specific length of time of exposure to an agent and the drug category was observed (Ertz-Archambault et al., 2017). When investigating possible mechanistic links between chronic inflammation and MDS, it is worth mentioning that over the last few years, aberrant innate immune activation and proinflammatory signaling within the malignant clone and the bone marrow microenvironment were advocated as key pathogenic drivers of MDS. Among them, S100A9-mediated NOD-like receptor protein 3 (NLRP3) inflammasome activation drives pyroptosis, an inflammatory and lytic form of cell death underlying many of the hallmark features of this disorder. This mechanism, along with the release of other danger-associated molecular patterns, expands bone marrow myeloid-derived suppressor cells, thus creating a feed-forward process and therefore propagating inflammasome activation (Sallman and List, 2019).

3. Response of autoimmune manifestations to therapies for MDS

The biological link existing between MDS clones and the occurrence of autoimmune manifestations is somehow mirrored by the described responses of the latter after MDS modifying therapeutic approaches, as shown in Table 3. 5-Azacytidine and haematopoietic stem cell transplantation (SCT) have been more often reported in this context.

3.1. Azacytidine

Azacytidine is a pivotal therapeutic option for patients with MDS (Fenaux et al., 2009). Noteworthy, beside the well known effects on bone marrow precursors, it is able to influence T-cell polarization both in vivo and in vitro (Bontkes et al., 2012) as well to modulate function and number of regulatory T cells (Treg) (Costantini et al., 2013). Even more interestingly, this drug modulates the sensitivity of cancer cells to cytotoxic T-cells (Gang et al., 2014). All these premises have even prompted the possible use of Azacytidine as a possible immune-therapeutic tool in the post- transplant setting (Sánchez-Abarca et al., 2010). Therefore not unexpectedly most of the T-cell abnormalities observed in MDS patients (Fozza et al., 2009; Fozza and Longinotti, 2012) tend to revert during therapy with Azacytidine, especially within the CD4+ subset (Fozza et al., 2015).

When focusing on the potential beneficial effects on AD, the first reports described MDS patients showing a complete response of deep neutrophilic dermatosis (Raj et al., 2007) and an improvement of

Table 3
Response of autoimmune manifestations to therapies for MDS.

Autoimmune disorder	Treatment	n	Outcome	Reference	Correlatives for response
antiphospholipid syndrome	azacytidine	1	CR	(Fraison et al., 2016)	NA
Behcet disease	azacytidine	6	2 improvement 3 CR 1 PR	(Tanaka et al., 2013) (Endo et al., 2015) (Fraison et al., 2016)	NA
fluctuating lupus-like symptoms	azacytidine	1	CR	(Frietsch et al., 2014)	NA
giant cell arteritis	azacytidine	2	CR	(Fraison et al., 2016)	NA
inflammatory bowel disease	azacytidine	1	CR	(Kono et al., 2018)	disappearance of multiple round ulcers mirrored by a marked decreased expression of tumour necrosis factor-α, interleukin-12 and interleukin-17 in colonic biopsy samples
neutrophilic dermatosis	azacytidine	2	CR	(Raj et al., 2007) (Kudo et al., 2017)	reduction in the level of the inflammatory marker matrix metalloproteinase-3
polyarthritis	azacytidine	3	CR	(Pilorge et al., 2011) (Fraison et al., 2016)	NA
polychondritis	azacytidine	5	5 CR 1 PR	(Fraison et al., 2016) (Fraison et al., 2016)	NA
polymyalgia rheumatica	azacytidine	4	2 CR 2 NR	(Fraison et al., 2016)	NA
seronegative rheumatoid arthritis	azacytidine	1	CR	(Frietsch et al., 2014)	NA
Sjogren disease	azacytidine	1	CR	(Fraison et al., 2016)	NA
small vessel vasculitis	azacytidine	1	NR	(Fraison et al., 2016)	NA
Still's disease	azacytidine	1	PR	(Fraison et al., 2016)	NA
Sweet's syndrome	azacytidine	4	CR	(Pilorge et al., 2011) (Frietsch et al., 2014) (Fraison et al., 2016)	NA
systemic lupus erythematosus	azacytidine	3	CR	(Al Ustwani et al., 2011) (Fraison et al., 2016)	reduction in the frequency of regulatory T cells
Vasculitis	azacytidine	3	CR	(Pilorge et al., 2011) (Frietsch et al., 2014) (Fraison et al., 2016)	NA
Behcet disease	aSCT	5	CR	(Yamato, 2003) (Tomonari et al., 2004) (Nonami et al., 2007) (Kook et al., 2014) (Lee et al., 2017)	NA
Pyoderma Gangrenosum	aSCT	1	improvement	(Lee et al., 2017)	NA
polyarteritis nodosa	aSCT	1	CR	(Stavenga et al., 2016)	NA
relapsing polychondritis	aSCT	1	CR	(Tomomatsu et al., 2012)	NA
seronegative symmetrical synovitis	aSCT	1	CR	(Ishii et al., 2016)	NA
spondyloarthritis	aSCT	1	CR	(Simonetta et al., 2015a)	NA
Takayasu arteritis	aSCT	1	CR	(Kato et al., 2014)	NA

List of abbreviations: allogeneic stem cell transplantation (aSCT), complete response (CR), no response (NR), not applicable (NA), partial remission (PR).

systemic lupus erythematosus (SLE) after treatment, which was interestingly paralleled by a reduction in the frequency of Treg (Al Ustwani et al., 2011). Also BD was shown to significantly improve with Azacytidine (Tanaka et al., 2013; Endo et al., 2015). In two following reports describing 3 and 4 patients respectively, different autoimmune conditions were reported to respond to this hypomethylating agent, such as Sweet's syndrome (Pilorge et al., 2011; Frietsch et al., 2014), polyarthritis (Pilorge et al., 2011), vasculitis (Pilorge et al., 2011; Frietsch et al., 2014) as well as seronegative rheumatoid arthritis and fluctuating lupus-like symptoms (Frietsch et al., 2014). Further responses were more recently reported in patients once again with neutrophilic dermatosis, along with a reduction in the level of the inflammatory marker matrix metalloproteinase-3 (Kudo et al., 2017), relapsing polychondritis (Erden et al., 2018) and inflammatory bowel disease (Kono et al., 2018). In the latter, the disappearance of multiple round ulcers was mirrored by a marked decreased expression of tumour necrosis factor-α, interleukin-12 and interleukin-17 in colonic biopsy samples, suggesting that the efficacy of Azacytidine in improving this AD was based on the suppression of pro-inflammatory cytokine responses (Kono et al., 2018). In most of these patients autoimmune conditions were resistant to several lines of immunosuppressive therapy and their improvement was usually paralleled by the haematological response to Azacytidine.

In the largest available study the efficacy of Azacytidine on AD was retrospectively assessed in 22 patients with MDS or CMML. Responses of a wide range of AD to Azacytidine 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 AD was parallel in 13 cases (59%), being both favourable in 11 cases and both unfavourable in 2. All responses of AD to Azacytidine were observed by the third cycle, although about one third of responses improved and became complete between 3 and 6 cycles. Noteworthy, 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 describing 11 patients treated with Azacytidine, responses of their AD were recorded in 9/11 (80%) and 6/11 (55%) patients at 3 and 6 months, respectively (Mekinian et al., 2016).

All these findings suggest that this hypomethylating agent is able to

beneficially modulate some of the AD associated with MDS. It is still necessary to delineate the mechanisms underlying such an improvement as we may hypothesize either an indirect impact based on the control of the MDS clone or a direct immunomodulatory activity.

3.2. Stem cell transplantation

SCT is very well known to induce an overall immune reprogramming which has even lead to suggest a possible therapeutic application for the management of AD. This is especially true for autologus SCT but also allogeneic SCT has to be considered for carefully selected cases (Snowden et al., 2017). It is more often reserved to younger patients with high risk diseases for which fully myeloablative and reduced intensity conditioning essentially offer similar outcomes (Scheid et al., 2017). When considering that only few MDS patients are candidate to allogenic SCT and that AD are a possible contraindication to transplantation, it is worth mentioning that the resolution of concomitant AD has been reported after SCT in some patients. The condition most often reported in this field was BD, which was resolved after cord blood SCT in 3 patients (Yamato, 2003; Tomonari et al., 2004; Nonami et al., 2007) and after peripheral blood SCT in one patient each with fully myeloablative (Kook et al., 2014) or reduced intensity conditioning (Lee et al., 2017). In the latter case BD was associated with Pyoderma Gangrenosum which also improved (Lee et al., 2017). Interestingly also relapsing polychondritis was reported to respond to non myeloablative SCT (Tomomatsu et al., 2012), Takayasu arteritis (Kato et al., 2014) and remitting seronegative symmetrical synovitis (Ishii et al., 2016) to cord blood SCT whereas spondyloarthritis (Simonetta et al., 2015a) and polyarteritis nodosa (Stavenga et al., 2016) to fully myeloablative SCT. Similarly to what reported for Azacytidine, the resolution of AD after SCT was almost always associated with the efficacy of transplantation towards the MDS clone. As already mentioned, very few data are available in this context. However, when considering the limited fraction of patients with concomitant MDS and AD undergoing SCT beside the clinical improvements reported in different immune-mediated conditions, we suggest that the possible impact of SCT on MDS-associated AD should be further investigated within the already available transplant registries including MDS patients.

4. Response of autoimmune disorders to immunotherapy

Apart from the above mentioned improvements of MDS-associated AD after therapies specific for MDS, their outcome has been specifically addressed after more conventional immune-therapeutic approaches. In particular a French multicenter retrospective study assessed the efficacy and safety of different biologics such as TNF-α antagonists, tocilizumab, rituximab and anakinra for systemic inflammatory and AD associated with MDS. Noteworthy when multiple lines of treatment were applied, data were analyzed before and at the end of each line and were pooled to compare overall responses. Among the 29 included patients 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 in the whole cohort: steroids alone (22%), disease-modifying antirheumatic drugs (23%), TNF-α antagonists (14%), anakinra (10%), rituximab (10%), tocilizumab (7%) and azacytidine (9%). When considering all 114 lines, overall responses were observed in 54% cases and were more frequent with steroids (78%) and rituximab (66%) than after disease-modifying antirheumatic drugs (45%) and other biologics (33%). Moving to specific conditions, 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). These data confirm that, even though a fraction of patients with concomitant MDS and AD can be potentially managed with conventional immune-therapeutic treatments, some of these autoimmune manifestations display unsatisfactory responses to such an approach, further highlighting the potential value of clinical responses obtained with MDS-modifying drugs.

5. The other side of the coin

When considering a specular point of view, haematologic improvements have been observed in some MDS patients receiving immunosuppressive treatments for their AD. Such results have been reported anecdotally in patients receiving methotrexate for dermatomyositis (Tsuji et al., 2003) or rituximab for SLE (Simonetta et al., 2015b) but also more systematically when response to immunosuppressive therapy was assessed in 30 patients with AD associated with MDS, among which the most frequent clinical manifestations were skin vasculitis and arthritis. Overall AD responded to immunosuppressive therapy (primarily prednisone) in 26/27 patients treated. Quite unexpectedly, cytopenias improved substantially in 6 patients, including complete normalization of peripheral blood counts in 2 patients with cytogenetic remission in one. Noticeably patients with haematological responses to immunosuppressive therapy showed improved survival. On the other side the AD was implicated as a primary cause of death in 8/17 patients who died, further highlighting the relevant clinical role exerted by these associated conditions in patients with MDS (Enright et al., 1995). Although these findings are obtained within a single study involving a limited number of patients, taking into account the strong pathogenetic and therapeutic interplays between MDS and AD, they would deserve to be more systematically addresses in a prospective manner or in the context of already available registries including MDS patients.

It is worth mentioning that, apart from the reported haematologic improvements observed in some MDS patients receiving immunosuppressive treatments for their AD, several immune-modulating approaches are routinely used to directly tackle dysplastic hemopoiesis. Even though the first results in this context were obtained with antithymocyte globulin (Molldrem et al., 1997), several other drugs have offered extremely promising responses. 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) but potentially also in the high risk setting (Adès et al., 2009). 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 (Mc Daniel et al., 2012). Several other immune-modulating strategies have been specifically tested in MDS patients with various results. Among them checkpoint inhibitors have been widely studied and are approved for several solid tumours and other hematologic malignancies. Besides cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), T-cell immune checkpoints, such as T-cell immunoglobulin mucin-3 (TIM-3) and lymphocyte activation gene-3 (LAG-3) as well as macrophage checkpoint CD47 are also under investigation as therapeutic targets for AML and MDS (Liu et al., 2019). Interestingly also INCB024360, an oral inhibitor of the enzyme indoleamine 2,3-dioxygenase (IDO), which catalyzes the degradation of tryptophan to kynurenine, increases T cell proliferation and decreases T regulatory cells and myeloid derived suppressor cells suppressive activity, has shown potential activity within a phase II study (Komrokji et al., 2019).

6. Conclusions

Even in the context of a pathogenesis dominated by well defined molecular defects, over the last few years several findings have underlined the role of different immune pathways and mechanisms in the biological and clinical scenario of MDS patients. One of the most striking demonstration of this link is depicted by the improvement of

AD after disease-modifying therapeutic approaches for MDS. On the other side the deep interconnection between these two group of conditions is somehow corroborated by the observation that at least in a fraction of MDS patients haematologic improvements can be observed with immune-therapeutic approaches or even with immunosuppressants administered to tackle their AD. Such a specular behaviour may further strengthen the hypothesis that, like yin and yang, MDS and AD represent clinical conditions which can broadly influence and modulate each other. Additional studies should help to elucidate which specific mechanisms sustain the preferential development of AD in MDS patients and if specific disease subgroups or molecular defects are more often associated with AD, in order to delineate the biological premises for new therapeutic approaches.

Declaration of Competing Interest

Nothing to declare.

References

Adès, L., Boehrer, S., Prebet, T., et al., 2009. Efficacy and safety of lenalidomide in intermediate-2 or high-risk myelodysplastic syndromes with 5q deletion: results of a phase 2 study. Blood 113, 3947–3952.

Al Ustwani, O., Francis, J., Wallace, P.K., Ambrus Jr, J., Wetzler, M., 2011. Treating myelodysplastic syndrome improves an accompanying autoimmune disease along with a reduction in regulatory T-cells. Leuk. Res. 35 (5), e35–36.

Anderson, L.A., Pfeiffer, R.M., Landgren, O., Gadalla, S., Berndt, S.I., Engels, E.A., 2009. Risks of myeloid malignancies in patients with autoimmune conditions. Br. J. Cancer 100 (5), 822–828.

Billström, R., Johansson, H., Johansson, B., Mitelman, F., 1995. Immune-mediated complications in patients with myelodysplastic syndromes: clinical and cytogenetic features. Eur. J. Haematol. 55 (1), 42–48.

Bontkes, H.J., Ruben, J.M., Alhan, C., Westers, T.M., Ossenkoppele, G.J., van de Loosdrecht, A.A., 2012. Azacitidine differentially affects CD4(pos) T-cell polarization in vitro and in vivo in high risk myelodysplastic syndromes. Leuk. Res. 36 (7), 921–930.

Costantini, B., Kordasti, S.Y., Kulasekararaj, A.G., Jiang, J., Seidl, T., Abellan, P.P., et al., 2013. The effects of 5-azacytidine on the function and number of regulatory T cells and T-effectors in myelodysplastic syndrome. Haematologica 98, 1196–1205.

de Hollanda, A., Beucher, A., Henrion, D., et al., 2011. Systemic and immune manifestations in myelodysplasia: a multicenter retrospective study. Arthritis Care Res. 63 (8), 1188–1194.

Endo, M., Sekikawa, A., Tsumura, T., Maruo, T., Osaki, Y., 2015. A case of myelodysplastic syndrome with intestinal Behçet's disease like symptoms treated by prednisolone and azacitidine. Am. J. Case Rep. 16, 827–831.

Enright, H., Jacob, H.S., Vercellotti, G., Howe, R., Belzer, M., Miller, W., 1995. Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: response to immunosuppressive therapy. Br. J. Haematol. 91 (2), 403–408.

Erden, A., Bilgin, E., Kılıç, L., Sarı, A., Armağan, B., Büyükaşık, Y., et al., 2018. Remission of relapsing polychondritis after successful treatment of myelodysplastic syndrome with azacitidine: a case and review of the literature. Drug Metab. Pers. Ther. 33 (2), 105–108.

Ertz-Archambault, N., Kosiorek, H., Taylo, G.E., et al., 2017. Association of therapy for autoimmune disease with myelodysplastic syndromes and acute myeloid leukemia. JAMA Oncol. 3 (7), 936–943.

Fenaux, P., Mufti, G.J., Hellstrom-Lindberg, E., Santini, V., Finelli, C., Giagounidis, A., et al., 2009. 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. 10 (3), 223–232.

Fenaux, P., Giagounidis, A., Selleslag, D., et al., 2011. MDS004 Lenalidomide del-5q Study Group. A randomized phase 3 study of Lenalidomide versus placebo in RBC transfusion-dependent patients with Low/Intermediate-1risk myelodysplastic syndromes with del-5q. Blood 118, 3765–3776.

Fozza, C., 2018a. The burden of autoimmunity in myelodysplastic syndromes. Hematol. Oncol. 36 (1), 15–23.

Fozza, C., 2018b. Deciphering the prognostic significance of autoimmune disorders in myelodysplastic syndromes. Ann. Hematol [Epub ahead of print].

Fozza, C., Longinotti, M., 2012. Are T-cell dysfunctions the other side of the moon in the pathogenesis of myelodysplastic syndromes? Eur. J. Haematol. 88 (5), 380–387.

Fozza, C., Longinotti, M., 2013. The role of T-cells in the pathogenesis of myelodysplastic syndromes: passengers and drivers. Leuk. Res. 37 (2), 201–203.

Fozza, C., Contini, S., Galleu, A., Simula, M.P., Virdis, P., Bonfigli, S., et al., 2009. Patients with myelodysplastic syndromes display several T-cell expansions, which are mostly polyclonal in the CD4(+) subset and oligoclonal in the CD8(+) subset. Exp. Hematol. 37 (8), 947–955.

Fozza, C., Longu, F., Contini, S., Galleu, A., Virdis, P., Bonfigli, S., et al., 2012a. Patients with early-stage myelodysplastic syndromes show increased frequency of CD4+CD25+CD127(low) regulatory T cells. Acta Haematol. 128 (3), 178–182.

Fozza, C., Contini, S., Virdis, P., Galleu, A., Massa, A., Bonfigli, S., et al., 2012b. Patients with myelodysplastic syndromes show reduced frequencies of CD4(+) CD8(+) double-positive T cells. Eur. J. Haematol. 88 (1), 89–90.

Fozza, C., Corda, G., Barraqueddu, F., Virdis, P., Contini, S., Galleu, A., et al., 2015. Azacitidine improves the T-cell repertoire in patients with myelodysplastic syndromes and acute myeloid leukemia with multilineage dysplasia. Leuk. Res. 39 (9), 957–963.

Fozza, C., Crobu, V., Isoni, M.A., Dore, F., 2016. The immune landscape of myelodysplastic syndromes. Crit. Rev. Oncol. Hematol. 107, 90–99.

Fraison, J.B., Mekinian, A., Grignano, E., Kahn, J.E., Arlet, J.B., Decaux, O., et al., 2016. Efficacy of Azacitidine in autoimmune and inflammatory disorders associated with myelodysplastic syndromes and chronic myelomonocytic leukemia. Leuk. Res. 43, 13–17.

Frietsch, J.J., Dornaus, S., Neumann, T., Scholl, S., Schmidt, V., Kunert, C., et al., 2014. Paraneoplastic inflammation in myelodysplastic syndrome or bone marrow failure: case series with focus on 5-azacytidine and literature review. Eur. J. Haematol. 93 (3), 247–259.

Gang, A.O., Frøsig, T.M., Brimnes, M.K., Lyngaa, R., Treppendahl, M.B., Grønbæk, K., et al., 2014. 5-Azacytidine treatment sensitizes tumor cells to T-cell mediated cytotoxicity and modulates NK cells in patients with myeloid malignancies. Blood Cancer J. 4, e197.

Giannouli, S., Voulgarelis, M., Zintzaras, E., Tzioufas, A.G., Moutsopoulos, H.M., 2004. Autoimmune phenomena in myelodysplastic syndromes: a 4-yr prospective study. Rheumatology (Oxford) 43 (5), 626–632.

Ishii, H., Konuma, T., Ohnuma, K., Hosono, O., Tanaka, H., Kato, S., et al., 2016. Remission of remitting seronegative symmetrical synovitis with pitting edema after unrelated cord blood transplantation for myelodysplastic syndrome. Ann. Hematol. 95 (3), 523–524.

Kato, H., Onishi, Y., Nakajima, S., Okitsu, Y., Fukuhara, N., Fujiwara, T., et al., 2014. Significant improvement of Takayasu arteritis after cord blood transplantation in a patient with myelodysplastic syndrome. Bone Marrow Transplant. 49 (3), 458–459.

Komrokji, R.S., Kulasekararaj, A., Al Ali, N.H., Kordasti, S., Bart-Smith, E., Craig, B.M., et al., 2016. Autoimmune diseases and myelodysplastic syndromes. Am. J. Hematol. 91 (5), E280–3.

Komrokji, R.S., Wei, S., Mailloux, A.W., et al., 2019. A phase II study to determine the safety and efficacy of the oral inhibitor of indoleamine 2,3-dioxygenase (IDO) enzyme INCB024360 in patients with myelodysplastic syndromes. Clin. Lymphoma Myeloma Leuk. 19, 157–161.

Kono, M., Komeda, Y., Sakurai, T., Okamoto, A., Minaga, K., Kamata, K., et al., 2018. Induction of complete remission by Azacitidine in a patient with myelodysplastic syndrome-associated inflammatory bowel disease. J. Crohns Colitis 12 (4), 499–502.

Kook, M.H., Yhim, H.Y., Lee, N.R., Song, E.K., Kim, H.S., Yim, C.Y., et al., 2014. Successful treatment of myelodysplastic syndrome and Behcet colitis after allogeneic hematopoietic stem cell transplantation. Korean J. Intern. Med. 29 (1), 123–125.

Kristinsson, S.Y., Björkholm, M., Hultcrantz, M., Derolf, ÅR., Landgren, O., Goldin, L.R., 2011. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. J. Clin. Oncol. 29 (21), 2897–2903.

Kudo, D., Shimizu, M., Kuroda, A., Suyama, T., Shinagawa, A., Ito, S., 2017. Myelodysplastic syndrome with neutrophilic dermatosis successfully treated with azacitidine. Rinsho Ketsueki 58 (6), 607–612.

Lee, S.J., Park, J.K., Lee, E.Y., et al., 2016. Certain autoimmune manifestations are associated with distinctive karyotypes and outcomes in patients with myelodysplastic syndrome: a retrospective cohort study. Medicine (Baltimore) 95 (13), e3091.

Lee, S.S., Ahn, J.S., Yun, S.J., Park, D.J., 2017. Successful treatment of a patient with myelodysplastic syndromeaccompanied by pyoderma gangrenosum and Behçet's disease using allogeneic stem cell transplantation. Blood Res. 52 (4), 319–321.

List, A., Kurtin, S., Roe, D.J., et al., 2005. Efficacy of lenalidomide in myelodysplastic syndromes. N. Engl. J. Med. 352, 549–557.

Liu, Y., Bewersdorf, J.P., Stahl, M., Zeidan, A.M., 2019. Immunotherapy in acute myeloid leukemia and myelodysplastic syndromes: the dawn of a new era? Blood Rev. 34, 67–83.

Marisavljević, D., Kraguljac, N., Rolović, Z., 2006. Immunologic abnormalities in myelodysplastic syndromes: clinical features and characteristics of the lymphoid population. Med. Oncol. 23 (3), 385–391.

Mc Daniel, J.M., Zou, J.X., Fulp, W., et al., 2012. Reversal of T-cell tolerance in myelodysplastic syndrome through lenalidomide immune modulation. Leukemia 26, 1425–1429.

Mekinian, A., Grignano, E., Braun, T., et al., 2016. Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. Rheumatology (Oxford) 55 (2), 291–300.

Mekinian, A., Dervin, G., Lapidus, N., Kahn, J.E., Terriou, L., Liozon, E., et al., 2017. Biologics in myelodysplastic syndrome-related systemic inflammatory and autoimmune diseases: French multicenter retrospective study of 29 patients. Autoimmun. Rev. 16 (9), 903–910.

Molldrem, J.J., Caples, M., Mavroudis, D., Plante, M., Young, N.S., Barrett, A.J., 1997. Antithymocyte globulin for patients with myelodysplastic syndrome. Br. J. Haematol. 99 (3), 699–705.

Montoro, J., Gallur, L., Merchán, B., et al., 2018. Autoimmune disorders are common in myelodysplastic syndrome patients and confer an adverse impact on outcomes. Ann. Hematol. 97 (8), 1349–1356.

Nonami, A., Takenaka, K., Sumida, C., Aizawa, K., Kamezaki, K., Miyamoto, T., et al., 2007. Successful treatment of myelodysplastic syndrome (MDS)-related intestinal Behçet's disease by upfront cord blood transplantation. Intern. Med. 46 (20), 1753–1756.

Okamoto, T., Okada, M., Mori, A., et al., 1997. Correlation between immunological abnormalities and prognosis in myelodysplastic syndrome patients. Int. J. Hematol. 66

(3), 345–351.
Papaemmanuil, E., Gerstung, M., Malcovati, L., Tauro, S., Gundem, G., Van Loo, P., et al., 2013. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 122 (22), 3616–3627.
Pilorge, S., Doleris, L.M., Dreyfus, F., Park, S., 2011. The autoimmune manifestations associated with myelodysplastic syndrome respond to 5-azacytidine: a report on three cases. Br. J. Haematol. 153 (5), 664–665.
Raj, K., Ho, A., Creamer, J.D., du Vivier, A.W., Salisbury, J.R., Mufti, G.J., 2007. Complete response of deep neutrophilic dermatosis associated with myelodysplastic syndrome to 5-azacytidine. Br. J. Dermatol. 156 (5), 1039–1041.
Sallman, D.A., List, A., 2019. The central role of inflammatory signaling in the pathogenesis of myelodysplastic syndromes. Blood 133, 1039–1048.
Sánchez-Abarca, L.I., Gutierrez-Cosio, S., Santamaría, C., Caballero-Velazquez, T., Blanco, B., Herrero-Sánchez, C., et al., 2010. Immunomodulatory effect of 5-azacytidine (5-azaC): potential role in the transplantation setting. Blood 115 (1), 107–121.
Scheid, C., de Wreede, L., van Biezen, A., Koenecke, C., Göhring, G., Volin, L., et al., 2017. Validation of the revised IPSS at transplant in patients with myelodysplastic syndrome/transformed acute myelogenous leukemia receiving allogeneic stem cell transplantation: a retrospective analysis of the EBMT chronic malignancies working party. Bone Marrow Transplant. 52, 1519–1525.
Seguier, J., Gelsi-Boyer, V., Ebbo, M., et al., 2019. Autoimmune diseases in myelodysplastic syndrome favors patients survival: a case control study and literature review. Autoimmun. Rev. 18 (1), 36–42.
Simonetta, F., Guerne, P.A., Tirefort, Y., Masouridi-Levrat, S., Roosnek, E., Chalandon, Y., 2015a. Complete and sustained remission of spondyloarthritis after allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome. Joint Bone Spine 82 (3), 216–217.
Simonetta, F., Posa, M., Villard, J., Marceau-Renaut, A., Preudhomme, C., Samii, K., et al., 2015b. Restoration of hematopoiesis in a case of myelodysplastic syndrome associated with systemic lupus erythematosus treated with rituximab. Ann. Hematol. 94 (7), 1247–1249.
Smith, M.A., Smith, J.G., 1991. The occurrence subtype and significance of haemopoietic inhibitory T cells (HIT cells) in myelodysplasia: an in vitro study. Leuk. Res. 15 (7), 597–601.
Snowden, J.A., Badoglio, M., Labopin, M., Giebel, S., McGrath, E., Marjanovic, Z., et al., 2017. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv. 1 (27), 2742–2755.
Stavenga, M., Leavis, H.L., de Witte, T.M., Raymakers, R.A., 2016. Allogeneic stem cell transplantation in a patient with myelodysplasticsyndrome and polyarteritis nodosa: a case report and systematic review. Ann. Hematol. 95 (4), 645–647.
Tanaka, H., Shimizu, N., Tougasaki, E., Kawajiri, C., Hashimoto, S., Takeda, Y., et al., 2013. Successful treatment by azacitidine therapy of intestinal Behçet's disease associated with myelodysplastic syndrome. Int. J. Hematol. 97 (4), 520–524.
Tomomatsu, J., Hamano, Y., Ando, J., Komatsu, N., Sugimoto, K., 2012. Non-myeloablative allogenic BMT for myelodysplastic syndrome successfully controlled accompanying relapsing polychondritis. Bone Marrow Transplant. 47 (5), 742–743.
Tomonari, A., Tojo, A., Takahashi, T., Iseki, T., Ooi, J., Takahashi, S., et al., 2004. Resolution of Behçet's disease after HLA-mismatched unrelated cord blood transplantation for myelodysplastic syndrome. Ann. Hematol. 83 (7), 464–466.
Tsuji, G., Maekawa, S., Saigo, K., Nobuhara, Y., Nakamura, T., Kawano, S., et al., 2003. Dermatomyositis and myelodysplastic syndrome with myelofibrosis responding to methotrexate therapy. Am. J. Hematol. 74 (3), 175–178.
Wilson, A.B., Neogi, T., Prout, M., Jick, S., 2014. Relative risk of myelodysplastic syndromes in patients with autoimmune disorders in the general practice research database. Cancer Epidemiol. 38 (October (5)), 544–549.
Yamato, K., 2003. Successful cord blood stem cell transplantation for myelodysplastic syndrome with Behçet disease. Int. J. Hematol. 77 (1), 82–85.
Zhao, S., Mao, H., Wang, H., Yu, J., 2002. The relationship between myelodysplastic syndromes and autoimmune disorders. Zhonghua Xue Ye Xue Za Zhi. 23 (6), 311–313.