CASE REPORT

IMMUNOSUPPRESSIVE TREATMENT WITH CYCLOSPORIN-A FOR A PATIENT WITH HYPOPLASTIC MYELODISPLASTIC SYNDROME: A CASE REPORT

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Abstract: Background: Immunosuppressive therapy with antithymocyte globulin (ATG), cyclosporine (CsA) or both has been shown to induce haematological responses in a subset of patients with myelodysplastic syndromes (MDS), in particular in the hypocellular form of MDS.

Case report: We report our first case with hypocellular MDS treated with CsA. A 54-year-old female referred to our Department due to weakness and severe pancytopenia. Hypocellular form of MDS was diagnosed after bone marrow biopsy. Treatment with CsA was started one year after diagnosis. Treatment with CsA resulted in clinical improvement, a very good partial haematological response, resolution of transfusion requirement and an increase in bone marrow cellularity.

Conclusions: In our experience, immunosuppressive treatment with CsA and/or ATG could be an alternative for patients with hypoplastic MDS for whom there is no possibility of allogenic bone marrow transplantation as only curative therapy.

Keywords: hypocellular myelodysplastic syndrome, pancytopenia, immunosuppressive therapy, cyclosporine A.

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematopoietic stem cell disorders characterized by dysplasia in one or more of the haematopoietic cell lines, ineffective haematopoiesis resulting in peripheral
cytopenias and progressive evolution to acute leukaemia [1, 2]. Patients with
MDS are older adults with comorbidities, and death from MDS is due to pro-
gression to acute leukaemia or to the consequences of cytopenia [3]. The Inter-
national Prognostic Scoring System (IPSS) can predict survival based on clin-
ical, haematological and karyotypic features [4]. The only curative treatment for
MDS is allogenic bone marrow transplantation combined with aggressive che-
motherapy [5], but due to the older age of the patients with MDS it is rarely a
possible therapeutic approach. Most of the patients are treated with support-
ive care [6], haematopoietic growth factors [7], decitabine [8], lenalidomide [9], or
immunosuppressive therapy with antithymocyte globulin and/or cyclosporine
[10, 11] etc.

The bone marrow in patients with MDS is usually hypercellular or normo-
cellular with dysplastic characteristics. However, some investigators have repor-
ted MDS with hypocellular bone marrow with dysplastic hematopoiesis as a
separate clinicopathologic entity [12, 13]. It is characterized by severe thrombo-
cytopenia, leucopenia and/or anaemia; karyotypic abnormalities are usually
absent. Some authors consider hypoplastic MDS a subtype of aplastic anaemia
(AA) [14]. Because hypoplastic MDS may be due to immune reaction against
haematopoietic stem cells, and usually is not responsive to conventional ther-
apy, there might be a role for immunosuppressive therapy (IST) such as antithy-
mocyt globulin (ATG) or cyclosporine (CsA) in the treatment of this form of
MDS [10, 11]. Immunosuppressive therapy has been shown to induce sustained
haematological responses in a subset of patients with MDS. In this article, we
report the first case of MDS treated with immunosuppressive therapy with CsA
in our institution.

Case Report

A 54-year-old female, referred to our Department in May 2007 due to
weakness and severe pancytopenia without any previous medical history. Her
haemoglobin level was 68 g/L, leucocytes 2.6 × 10⁹/L with absolute neutrophil
count (ANC) 1.2 × 10⁹/L, platelet count 49 × 10⁹/L, MCV 101 fL and normal
peripheral blood smear without blast or immature blood cells. The first bone
marrow biopsy showed extremely hypocellular bone marrow with rare myeloid
progenitors, pathohistological findings were severe hypoplastic anaemia and
agranulocytosis. Because of pathohistological findings highly suspicious of
aplastic anaemia, two weeks later we performed a contralateral iliac crest biopsy
with similar pathohistological findings (extremely hypocellular bone marrow
but with dysplastic characteristics of all three lineages, rare megakaryocytes and
blast cells < 5%, Figs 1 and 2). She was treated with red cell transfusions
almost every two weeks and corticosteroids (prednisone 1mg/kg), but with a
further decline of all haematological parameters. The platelet level decreased to \(4 \times 10^9/l\) and the clinical course was complicated by the appearance of haematomata and skin haemorrhagic syndrome.

![Figure 1](image1.png)

Figure 1 – Hypocellular bone marrow with elements of marrow dysplasia, stained with HE; \(\times 40\)

![Figure 2](image2.png)

Figure 2 – Hypocellular bone marrow with elements of marrow dysplasia, HE; \(\times 200\)

In August 2007 she went to a foreign Haematology Clinic in Germany where another bone marrow biopsy was performed. The histological finding was again a hypocellular form of myelodysplastic syndrome with normal karyotype (46, XX) and IPSS score intermediate 1. They suggested treatment with growth factors and immunosuppressive therapy with ATG and CsA. In the event of treatment failure, further therapy should be allogenic transplantation from human lymphocyte antigen (HLA) from an identical, related or unrelated donor.

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Because our patient has only one haploidentical sister and she refused to proceed directly with bone marrow transplantation from a matched unrelated donor, we started with treatment with growth factors (erythropoietin and granulocyte colony stimulating factors-GCSF) and continued with supportive treatment with red cell transfusions and corticosteroid therapy. In the period from June 2007 until June 2008 she received 24 units of packed red blood cell transfusions. Due to the erythropoietin treatment (4000 unit 3 × weekly), her haemoglobin level slowly increased to 100 g/L with a decrease in the number of red cell transfusions to one in two months. But the main problem was persistent and severe thrombocytopenia, resistant to corticosteroid treatment.

In June 2008 we started with immunosuppressive treatment with cyclosporine 200 mg per day and a low dose of prednisone (20mg/day). Treatment with erythropoietin and GSCF continued. Six months after the initiation of the cyclosporine therapy a good partial haematological response was achieved. She no longer required red cell transfusions, treatment with GCSF was stopped and she continued only with CsA (200 mg twice daily), prednisone 5mg per day and erythropoietin (4000 U, 3 × weekly). Her haemoglobin level during the last two years was between 116 and 134 g/L, leukocyte number between 3.7 and 5.1 × 10^9/L with ANC higher than 1.5 × 10^9/L, and platelet count higher than 50 up to 125 × 10^9/L. Control bone marrow biopsy was performed in June 2010 with the histological finding of hypocellular myelodysplastic syndrome but with a marked increase in cellularity compared to the previous biopsies (Figs 3, 4 and 5). Her last haemogram in February 2010 showed a haemoglobin level of 124 g/L, leukocyte number 4.1 × 10^9/L with ANC 2.6 × 10^9/L, and platelet count 84 × 10^9/L.

![Figure 3 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, stained with HE; × 40](image-url)
Discussion

The combination of a hypocellular bone marrow with dysplasia of all three myeloid lineages is an intriguing problem for haematologists and pathologist in terms of classification and treatment. This combination has been described previously as hypocellular, hypoplastic or autoimmune MDS. Some authors classify hypoplastic MDS as AA, while others consider hypoplastic MDS as a
subgroup of MDS [12, 13]. Hypoplastic MDS is probably most accurately categorized as a distinct entity with features of both MDS and AA [12, 15, 16].

There is increasing evidence that immunological dysregulation play an important role in ineffective haematopoiesis and progressive cytopenia. Some authors suggest that hypoplastic MDS is caused by an autoimmune reaction similar to that in AA [15, 17]. This theory is supported by the low incidence of karyotypic abnormalities in patients with hypoplastic MDS as opposed to frequently observed karyotypic abnormalities in other clonal stem cell disorders. Patients with hypocellular MDS share an overlap of characteristics with patients with aplastic anaemia. There is skewing of CD4 : CD8 ratios, restricted T-cell receptor Vβ usage together with high plasma levels of tumour necrosis factor-α and interferon-γ indicating a T-cell mediated myelosupression [17–21].

Treatment with immunosuppressive agents like ATG, CsA or both cause clinical improvement (decline and resolution of transfusion requirement, decreased use of haematopoietic growth factors, partial or complete haematological response) in both patients with hypocellular MDS and AA. It has been shown in various studies that patients with hypocellular MDS and low-risk MDS have a higher response rate to immunosuppressive treatment with ATG and CsA and could benefit from this form of treatment, as compared with other patients with MDS [11, 22]. The persistence of dysplastic characteristics of bone marrow after immunosuppressive treatment, which was obvious in our case as well as in other trials, and the apparent need for continuous or repetitive administration of immunosuppressive therapy in patients with hypoplastic MDS, is in contrast to the often durable effect of a single course of ATG and CsA in a patient with AA.

Many trials using antithymocyte globulin or cyclosporine, alone or in combination, have reported responses ranging from zero to 30% in unselected patients [11–18, 22–24]. A recent open-labelled randomized phase III trial by Passweg J.R. et al. reported a significant response rate in 29% of patients with MDS treated with ATG+CsA versus supportive treatment only [23]. However, higher response rates were obtained when patients were selected for immunosuppressive treatment based on age, IPPS score, number of months of transfusion dependence and the presence of HLA-DR15 [17, 25].

Other immunosuppressive agents, targeting immune dysregulation in MDS, have also been used in the treatment of patient with MDS in the last few years. Olnes M.J. and Sloand E.M. recently reported the results of a pilot clinical trial [26] and a case report of a 56-year-old woman [27] with hypocellular MDS treated with alemtuzumab (anti CD52 antibody). After treatment with alemtuzumab, her blood cell counts returned to normal and she has remained in complete remission for more than 2 years of follow-up [27]. The overall response rate in this pilot clinical trial was 68% in 31 evaluable patients and the complete response rate was 18% [26].
In conclusion, MDS is remarkably heterogeneous in its clinical presentation, morphology, and risk of progression to acute leukaemia. Recent advances have shown that immune dysregulation contributes to disease pathobiology in selected patients. Our experience with immunosuppressive treatment of a patient with hypocellular MDS is similar to already reported results which confirmed that bone marrow cellularity and low IPSS are important factors predicting response to ATG and CsA. Further studies on the pathogenesis and immunological factors influencing the etiopathogenesis of MDS will identify patients who will respond best to immunosuppressive therapy, as well as establishing the most appropriate IST for each individual.

REFERENCES

Резиме

ИМУНОСУПРЕСИВЕН ТРЕТМАН СО ЦИКЛОСПОРИН-А КАЈ ПАЦИЕНИТИ СО ХИПОПЛАСТИЧЕН МИЕЛОДИСПЛАСТИЧЕН СИНДРОМ: ПРИКАЗ НА СЛУЧАЈ

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Абстракт: Имуносупресивната терапија со антитимоцитен глобулин (АТГ) и/или циклоспорин-А (ЦсА) може да индуцираат хематолошки одговор кај одредена група на болни со миелодиспластичен синдром (МДС), особено кај болни со хипоцелуларна форма на МДС.

Во овој труд реферираме случај со хипоцелуларен МДС лекуван со циклоспорин. Се работи за 54 години жена, која се јавила на нашата Клиника поради слабост и тешка панцитопенија. Биопсијата на коска потврди дека се работи за хипоцелуларна форма на МДС. Третманот со циклоспорин-А затпочна една година по иницијалната дијагноза и претходниот супортивен третман. Терапијата со циклоспорин-А доведе до кlinично подобрување на состојбата, многу добар парцијален хематолошки одговор, зголемување на целуларноста на коскената срцевина и намалување на потребата од супортивен третман, особено на трансфузизите на еритроцити.

Нашето искуство покажа дека имunosупресивната терапија со ЦсА и/или АТГ може да бидат альтернатива во третманот на болните со хипоцелуларна форма на МДС, особено за болните за кои не е можна алгената трансплантација, како единствена куративна метода за ова заболување.

Ключни зборови: хипоцелуларен миелодиспластичен синдром, панцитопенија, имunosупресивна терапија, циклоспорин-А.

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Figure 3 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, stained with HE; × 40
Figure 4 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, HE; × 200

Figure 5 – Normocellular bone marrow with elements of marrow dysplasia, HE; × 400