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Outcomes and mutational analysis of patients with lower-risk non-del5q myelodysplastic syndrome treated with antithymocyte globulin with or without ciclosporine A☆

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ABSTRACT

Immunosuppressive treatment is a disease-modifying therapy for lower-risk myelodysplastic syndromes (MDS). However, IST is relatively rarely used and long-term outcomes of patients are seldom reported. We retrospectively studied outcomes of 20 patients with lower-risk non del 5q MDS with transfusion dependency, with horse or rabbit antithymocyte globulin ± ciclosporine A, and frontline eltrombopag in two of them. IPSS-R was low, intermediate and high in 30%, 55% and 10% of the patients, respectively. Fifty-five percent of the patients had hypocellular bone marrow (BM). Baseline mutations were detected in 31.5% of the patients and were more frequent in patients with normo/hypercellular MDS than in patients with hypocellular MDS. Transfusion independence rate for both red blood cells (RBC) and platelets was achieved in 45% of patients. RBC transfusion duration ≤6 months, B-cell counts > 0.2 G/L and, marginally, BM blasts ≤2% were associated with higher transfusion independence rate. Age and cellularity did not influence the response rate. Median transfusion independence duration was 53 months. Cumulative incidence of progression to a more aggressive myeloid disease was 0 in patients without baseline mutations and 33% in patients with baseline mutations (P = .008). Median progression-free and overall survival after treatment onset and median overall survival after loss of transfusion independence were 45.5 months, 68 months and not reached, respectively. In conclusion, antithymocyte globulin ± ciclosporine A results in durable responses in MDS, irrespective of age, in patients with lower-risk disease without B-cell lymphopenia and treated early in the course of the disease.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological disorders characterized by bone marrow (BM) failure, dysplasia and clonality, often normal or increased cellularity, resulting in cytopenia(s), and sometimes in acute myeloid leukemia (AML) transformation. Growth factors such as erythropoiesis stimulating agents (ESAs) are the mainstay of treatment for anemia in lower-risk MDS patients, resulting in responses in two thirds of cases. However, ESAs do not address the need for bilineal or trilineal responses. In addition, median duration of erythroid response is approximately two years; as a result, a group of lower-risk MDS patients remain in need of therapy after a relatively short period of response to ESAs.

Immunosuppressive treatment (IST) with antithymocyte globulin

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(ATG) with or without ciclosporine A (CsA) has been initially used for the hypocellular sybtype of MDS [1–3], an entity difficult to distinguish from aplastic anemia [4], for which ATG and CsA is an established treatment [5–7]. In addition, ATG ± CsA is used for refractory cytopenia of childhood, which is usually accompanied by hypocellular BM [8]. Several studies showed that ATG ± CsA was effective in 25–45% of selected adult MDS patients with a median response duration of 10–36 months [9–20]. Predictive factors of response varied between studies and included younger age, shorter red blood cell (RBC) transfusion dependency, lower platelet counts, reduced BM cellularity and immune determinants overlapping with the pathophysiology of aplastic anemia, such as small paroxysmal nocturnal hemoglobinuria (PNH), large T-cell lymphocytes, the presence of a DRB1 15 allele (DR15) and T-cell activation profile. Various ATG preparations were used (rabbit ATG: Fresenius, Thymoglobulin; horse ATG: Lymphoglobulin, ATGAM), with the adjunction of CsA whenever possible taking account of vascular and renal comorbidities of elderly MDS patients. Other modalities of immunosuppressive treatment for MDS include CsA without ATG, etanercept and alemtuzumab, with probative results [19–24]. Follow-up in these studies was often limited, with the notable exception of the compiled National Institutes of Health studies [16].

Despite positive results, because of known side effects (type II and III hypersensitivity reactions, profound immunosuppression due to T cell depletion), ATG ± CsA use has been restricted however to patients selected on the basis of age, comorbidities and predictive factors of response. Only a minority of younger patients with hypocellular MDS were therefore preferentially offered ATG ± CsA, while patients with a more typical profile with regard to age and cellularity were often excluded from studies and clinical practice.

With the advent of next generation sequencing, the mutational profile of hypocellular MDS and aplastic anemia evolving to MDS [25–30], as well as mutations conferring genetic predisposition to MDS [31–38], have been unraveled. We used comprehensive cytogenetic and genetic data to study predictive factors of response and long term outcomes of lower-risk MDS patients treated with ATG ± CsA.

2. Material and methods

2.1. Patients

Consecutive patients with MDS treated with ATG ± CsA between 2005 and 2015 in our institution, were included in this retrospective study. Eligibility criteria were international prognosis score system (IPSS) low and int-1, absence of del 5q, transfusion-dependent anemia and at least one additional clinically relevant cytopenia (absolute neutrophil count < 0.5 G/L or platelet count < 50 G/L) and non-eligibility for immediate allogeneic hematopoietic stem cell transplantation. In addition to eligibility criteria, patients were selected based on the presence of one or more of the following parameters: i) known predictive factors [9,10,13–20], ii) cytopenias in more than one lineage, iii) severe thrombocytopenia, for which available treatments are scarce, iv) failure of previous treatments. All selected patients had several of the following, sometimes overlapping characteristics, specifically: Pancytopenia N = 12, bicytopenia N = 8, platelet count < 10 G/L N = 6, 10–20 G/L N = 3, and 20–50 G/L N = 10, age < 50 years N = 2, and 50–60 years N = 5, hypocellular MDS N = 11, DR15 N = 10, severe autoimmunity N = 2, cytogenetic abnormalities associated with aplastic anemia N = 2 (trisomy 8, del(13q)), failure of multiple previous treatments N = 5. IPSS and revised IPSS were calculated according to Greenberg et al. [39,40].

2.2. Diagnostic assessment

BM smears and biopsies were centrally reviewed according to [4]. Morphology was assessed on 1000 cells or, in cases of very low cellularity, at least 500 cells. On BM biopsies, age-matched cellularity, myeloid to erythroid ratio, number of megakaryocytes and dysmegakaryopoiesis, number of CD34+ cells, fibrosis, iron staining and edema were systematically evaluated. Age-matched cellularity was determined according to [4,41]. Specifically, patient's cellularity was compared to normal mean values per age group as defined in [42]. Values below the lower range i.e. < 20% for patients aged 50–70 years and < 10% for patients aged ≥70 years were considered to indicate hypocellular MDS.

Karyotype ± fluorescent in situ hybridization (FISH) was performed in all patients. PNH diagnosis was performed using a sensitive flow cytometry assay. The panel used included FLAER and GPI-linked protein staining on neutrophils, monocytes and red blood cells when required. The test complied to the criteria of the international recommendations published in 2010 [43] and consisted in an 8-color combination reaching a sensitivity of at least 0.01% on leukocytes and 0.005% on erythrocytes. Quality control insurance was achieved through the participation to the French program of PNH external proficiency testing [44].

2.3. Mutational analysis

BM ± peripheral blood mononuclear cells were used for next generation sequencing of the coding regions of the following genes: *GATA2* (exons 4–6), *ASXL1*, *CBL*, *DNMT3A*, *ETV6*, *EZH2*, *IDH1*, *IDH2*, *JAK2*, *KIT*, *KRAS*, *MPL*, *NPM1*, *NRAS*, *PHF6*, *PTPN11*, *RIT1*, *RUNX1*, *SETBP1*, *SF3B1*, *SRSF2*, *TET2*, *TP53*, *U2AF1*, *WT1*, *ZRSR2*. Mutational analysis was performed on samples immediately preceding ATG and, for some patients, during follow-up and, in particular, at disease progression.

2.4. Treatment

Horse ATG (Lymphoglobulin 0,75 mL/kg/day for 5 days or ATGAM 40 mg/kg/day for 4 days) or rabbit ATG (Thymoglobulin 3,75 mg/kg/day for 5 days) were used, depending on availability of products in Europe. When used, CsA was started on day 1 of ATG at the dose of 5 mg/kg/day divided to 2 doses, and was continued for about one year with aiming at trough levels of 100–200 µg/L. Corticosteroids were administered from day 1 of ATG and for 14 days, with tapering thereafter, in order to prevent serum sickness. The two patients treated most recently (UPN19 and UPN20) received in addition to horse ATG (ATGAM) + CsA, eltrombopag 50 mg/day for two weeks, then increased to a maximum dose of 150 mg/day for three months.

2.5. Response assessment

Red blood cell (RBC) and platelet transfusion independence and IWG 2006 response criteria for altering natural history of MDS (complete remission, partial remission, disease progression) and for hematological improvement were used [45].

2.6. Statistics

Predictive factors of response were tested by logistic regression. Overall survival, progression-free survival and response duration were calculated with the Kaplan-Meier method [46]. Progression to a higher risk myeloid disease (higher-risk MDS, MDS/myeloproliferative neoplasms (MPN), AML) was taken into account as competing risk according to [47]. Survival times were compared by using the Cox model [48,49]. Type I error was fixed at 5%. All tests were two-tailed. Statistical analyses were performed with R software package.

3. Results

3.1. Characteristics of the patients

Twenty patients received immunosuppressive treatment with