Response to cladribine in patient with systemic mastocytosis

Primena kladribina u lečenju bolesnika sa sistemskom mastocitozom

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Abstract

Introduction. Systemic mastocytosis is a heterogeneous group of hematological disorders characterized by accumulation of mast cells in different organs. Case report. A 41-year-old woman presented with a three-year history of fatigue, occasional diarrhea, mild fever, skin rash and splenomegaly. Laboratory results showed severe anemia and thrombocytopenia. Cytological and histological investigation of bone marrow showed a marked increase of mast cells infiltration with following immunophenotype: CD117+, CD68+, CD34-, MPO-, CD15-. She was treated with cladribine 0.15 mg/kg body weight from day 1 to day 5, a total of six cycles, and achieved a good partial response, transfusion independency and normalization of spleen size. Although the patient responded to the treatment, the relapse with splenomegaly and bicytopenia was observed after 10 months. Conclusion. Cladribine therapy was efficient in the patient with systemic mastocytosis but the response was transient, so there is the need to search for new therapeutic options and more effective strategies in the treatment of patients with aggressive mast cell disorders.

Key words: mastocytosis; cytodiagnosis; cladribine; remission induction; recurrence.

Introduction. Sistemska mastocitoza ubrjava se u heterogenu grupu hematoloških oboljenja, a karakteriše je nagomilavanje mast celija u različitim organima. Prikaz bolesnika. Prikazana je bolesnica, stara 41 godinu, koja je u poslednje tri godine imala simptome malaksalosti, povremene prolive, povišenu temperaturu, osip po koži i splenomegaliju. Laboratorijski nalazi pokazali su tešku anemiju i trombocitopeniju. Citološko i histološko ispitivanje kostne srži pokazalo je izraženu infiltraciju mast celijama sa immunofenotipom: CD117+, CD68+, CD34-, MPO-, CD15-. Bolesnica je lečena kladribinom u dozi od 0,15 mg/kg telesne mase, od prvog do petog dana, a dovršen je parcialni odgovor. Bolesnica nije zahtevala transfuzije i veličina sleznine se normalizovala. Iako je bolesnica povoljno reagovala na primenjenu terapiju, nakon 10 meseci došlo je do relapsa sa splenomegalijom i bicitopenijom. Zaključak. Terapija kladribinom je efikasna kod bolesnika sa sistemskom mastocitozom, ali odgovor na lečenje je prolazan. Potrebno je istraživanje novih terapijskih agenata i efikasnijih strategija u lečenju bolesnika sa agresivnim oblikom mastocitoze.

Key words: mastocitoza; citodiagnostika; kladribin; remisija, indukcija; recidiv.

Introduction

Systemic mastocytosis (SM) is a clonal, extremely rare disorder characterized by abnormal mast cell proliferation in different organs, including bone marrow, skin, gastrointestinal tract, liver, spleen and lymph nodes. After skin, bone marrow is the second most frequently involved organ, and its infiltration by mast cells can lead to bone pain, pancytopenia and pathologic fractures. The diagnosis of mastocytosis is based on histological and immunohistochemical examination of skin or bone marrow biopsy specimens. Recommended therapy for aggressive forms of SM consists of cytoreductive agents and interferon-alpha (IFN-alpha).

Case report

A 40 year-old Caucasian woman presented with a two-year history of fatigue, occasional diarrhea, mild fever and rash. Physical examination and laboratory investigation revealed maculopapular rash (Figure 1), mild splenomegaly, with mild anemia (hemoglobin 103 g/L) and thrombocytopenia 129 × 10^9/L. Skin biopsy showed mastocyte infiltration in the derm, and the diagnosis of cutaneous mastocytosis was established. The patient was treated with symptomatic therapy – histamine H1 and H2 receptor blockers. A year later the patient was admitted to the hospital with severe fatigue, diarrhea and rash. Clinical examination showed pale skin
with disseminated itching rash, splenomegaly 5 cm below the left costal margin. Ultrasonography and computed tomography (CT) scan showed splenomegaly 19 cm. Gastro-duodenoscopy showed friable duodenal mucosa with multiple erosions. Laboratory data revealed severe anemia with hemoglobin concentration of 59 g/L, thrombocytopenia 18 × 10^9/L, white cell blood count 5.1 × 10^9/L (differential leukocyte formula: myelocytes 1%, bands 3%, segmented 29%, eosinophils 3%, lymphocytes 51%, monocytes 13%, erythroblasts 21/100). Erythrocyte sedimentation rate was elevated (134 mm/h). Coagulation parameters and serum immunoglobulin concentration (IgG 10.6 g/L; IgA 1.9 g/L; IgM 1.51 g/L) were normal. Serum C-reactive protein 11.34 g/L (normal range 0–5 g/L) and β2 microglobulin level 2.45 mg/L (normal range 0.70–1.80 mg/L) were elevated. The level of serum histamine 0.79 µmol/L (normal range 0.36–0.66 µmol/L) and lactate dehydrogenase – LDH (786 U/L) were elevated. Serum ferritin was elevated, 743.0 µg/L (normal range 5.00–170.00 µ/L). Cytological investigation of bone marrow revealed a marked increase of mast cells. A trephine biopsy showed infiltration of bone marrow by monomorphic, spindle shaped mast cells, and moderate fibrosis of the bone marrow (Figure 2). These cells were PAS negative. Their immunophenotype was c-kit/CD117+, CD68+, CD34-, MPO-, CD15-, which is consistent with mast cells. Cytogenetic analysis revealed normal female karyotype 46, XX. Cultures of hematopoietic progenitor cells showed the increased number of CFU-GM colonies (colony-forming unit granulocyte macrophage), spontaneous growth of BFU-E (burst forming unit erythroid) and increased number of erythropoietin stimulated BFU-E, comparing to the control and the absence of CFU-MK (megakaryocyte progenitors). Skeletal radiography did not show abnormalities on the bones. Clinical presentation and laboratory findings were consistent with the diagnosis of systemic mastocytosis. The patient was treated with cladribine 0.15 mg/kg body weight from day 1 to day 5, a total of six cycles. The cycles were repeated after 4 weeks. The response was assessed according to the proposed criteria by Valent et al. 4. The patient achieved a good partial response with normalization of spleen size and a complete blood count (CBC). The response lasted 10 months, when relapse occurred, with splenomegaly and bicytopenia (anemia and thrombocytopenia). The patient was again transfusion-dependent, under treatment with H1 and H2 receptor blockers.

**Discussion**

Clinical manifestations of SM are very heterogeneous, ranging from indolent to aggressive course with multisystem involvement and short survival. Systemic mastocytosis can coexist with other primary hematological disorders, such as myelodysplastic syndrome, myeloproliferative disorder or malignant lymphoma 5.

Bone marrow biopsy in patients with SM often indicates an increase in mast cells. Mast cells typically infiltrate bone marrow and consequently affect peripheral blood. Before bone marrow sampling, the pathologist must be informed about the possible diagnosis. A typical mast cell has a spindle – shaped nucleus and fine eosinophilic granules, and characteristic immunophenotype features (tryptase+, CD117+). The spleen, liver and gastrointestinal tract are also frequently involved 6. In the presented patient cutaneous form of mastocytosis preceded systemic mastocytosis. The disease progressed, and aggressive course with multisystem involvement was developed. Bone marrow biopsy showed marked mast cell infiltration with specific immunophenotype (CD117+, CD68+), and bone marrow fibrosis grade II was found (Figure 2).
Until now there has been no curative treatment for SM. Patients with cutaneous or indolent systemic disease are treated symptomatically, using histamine H1 and H2 receptor blockers and disodium cromoglycate. Aggressive forms of SM are often associated with hematomal disorders and are treated with cytoreductive therapy. Interferon-alpha and cytostatic drugs have been applied\(^3\), but relatively little is known about the quality of responses to IFN-alpha. Cladribine was effective in the patient with IFN-alpha resistant SM\(^7\). Cladribine eliminates mast cell growth factors, as cytokines interleukin (IL) 3 and IL-4. The response to cladribine in the presented patient was remarkably fast, after the first cycle of cladribine, the histamine-related symptoms vanished, and after a sixth cycle regression of splenomegaly and pancytopenia were observed. The drug was well tolerated, with no side effects. After a 10-month good response the patient developed relapse. Positive effect of cladribine treatment in 10 patients with systemic mastocytosis was published by Kluin-Nelemans et al.\(^8\), but a complete remission was not achieved. Most patients treated with cladribine showed a rapid decrease of mast cell infiltration and very good clinical response, as we observed in the presented patient. In aggressive form of SM first line treatment with cladribine as single agent is effective, but disease often relapse.

Molecules targeting mutant kit tyrosine kinase are potential agents in treatment, and they are under investigation in clinical trials\(^9,10\).

**Conclusio**

Cladribine therapy was efficient in the patient with systemic mastocytosis but the response was transient, so there is the need to search for new therapeutic options and more effective strategies in the treatment of patients with aggressive mast cell disorders.

So far there has not been established the standard therapy for SM, and treatment has to be adjusted to the needs of the individual patient. Advances in understanding the molecular pathogenesis of systemic mastocytosis will lead to development of new therapeutic options.

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**REFERENCES**


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