Ann Hematol (2008) 87:505–508
DOI 10.1007/s00277-007-0430-3

LETTER TO THE EDITOR

# Mast cell leukemia: a report of ten cases

**Caterina Giovanna Valentini · Michela Rondoni · Enrico Maria Pogliani · Maria Teresa Van Lint · Chiara Cattaneo · Laura Marbello · Alessandro Pulsoni · Fiorina Giona · Giovanni Martinelli · Giuseppe Leone · Livio Pagano**

Received: 5 September 2007 / Accepted: 4 December 2007 / Published online: 3 January 2008


Dear Editor,

Systemic mastocytosis (SM) comprises a heterogeneous group of disorders characterized by proliferation and accumulation of mast cells (MC) in one or more organs. Mast cell leukemia (MCL) is an extremely rare subtype of SM defined by leukemic infiltration of bone marrow and other organs by atypical neoplastic MC, morphologically characterized by cytoplasmic extensions, eccentric oval nucleoli and hypogranulated cytoplasm, which could exhibit a more immature blast-like morphology with no signs of maturation, prominent nucleoli and fine nuclear chromatin. Flow cytometric analysis of neoplastic MC reveals detection of CD2 and/or CD25 antigen, CD117/kit, CD68 [1, 2]. This infiltration may lead to bone marrow myelofibrosis with hemopoietic insufficiency, organ dysfunction, bleeding and death after a median survival time of 6–7 months [2, 3]. Diagnostic criteria for MCL correspond to that used for diagnosis of SM, but also include a high percentage of bone marrow (≥20% of all nucleated cells) and circulating (≥10% of leukocytes) MC. According to the WHO consensus classification, cases of MCL with less than 10% circulating MC should be termed aleukemic variant [4]. The prognosis of disease is severe: Most patients (pts) survive less than 1 year and respond poorly to cytoreductive drugs or chemotherapy. A curative therapy is currently not available.

Over the years 1995–2006, in collaboration with 17 Italian hematological divisions, 36 cases of SM were observed: 13 aggressive SM, ten MCL, seven indolent SM and six SM with associated hematopoietic non-mast cell lineage disease, particularly one acute myeloid leukemia, three myeloproliferative disorders (one idiopathic myelofibrosis, one polycythemia vera and one essential thrombocytemia) and two low-grade B-cell lymphoma; however, we focused the attention only on the ten cases of MCL.

All centres were asked to report data about epidemiological, clinical features, treatments and outcome of their cases of MCL. Diagnostic features included hematological parameters with morphological examination of peripheral blood smears, bone marrow aspirate and bone marrow biopsy with an evaluation of MC infiltrate and immunophenotypic examinations of MC by flow cytometry. Furthermore, information about cytogenetic analysis, molecular biology analysis for the presence of the *c-kit* point

C. G. Valentini (✉) · G. Leone · L. Pagano
Istituto di Ematologia, Università Cattolica del Sacro Cuore,
Largo Francesco Vito, 1,
00168 Rome, Italy
e-mail: giovannavalentini@libero.it

M. Rondoni · G. Martinelli
Istituto di Ematologia L. e A. Seragnoli, Università di Bologna,
Bologna, Italy

E. M. Pogliani
Divisione di Ematologia, Ospedale S. Gerardo,
Monza, Italy

M. T. Van Lint
Centro Trapianti di Midollo, Ospedale S. Martino,
Genova, Italy

C. Cattaneo
Divisione di Ematologia, Spedali Civili di Brescia,
Brescia, Italy

L. Marbello
Divisione di Ematologia, Ospedale Niguarda Ca' Granda,
Milan, Italy

A. Pulsoni · F. Giona
Istituto di Ematologia, Università "La Sapienza",
Rome, Italy

mutation Asp-816-Val, clinical presentation of disease and possible instrumental and histological examinations were requested.

The pts were diagnosed and classified according to the WHO criteria, and response to therapy has been judged following the proposed criteria by Valent et al [4, 5]. Overall survival (OS) was measured from diagnosis to death or last follow-up. The last follow-up was December 2006. Kaplan–Meier method was used to analyze OS. The main clinical and biological features of pts with the different therapeutic approaches for each of them are reported in Tables 1 and 2.

The median age of pts was 56 years (range 43–74); a preponderance of the female gender was noted (female to male ratio 2.3:1). The percentage of circulating MC ranged from <1% to 31% of all leukocytes: In fact, three pts had typical MCL, while to the other seven, aleukemic MCL was diagnosed. Mild anemia was always present at diagnosis, and the hemoglobin concentration ranged from 8 to 11.09 g/dl (median value 11.03 g/dl).

Molecular biology studies were performed in eight of ten pts: six of eight (75%) showed the *c-kit* point mutation D816V, only one pt had completely negative molecular biology tests, while in another pt, a different silent *c-kit* mutation was found (C2415T). Cytogenetic analysis of bone marrow cells resulted normal in all but one pt, in which karyotype abnormalities were recognized (del 5q).

Extramedullary leukemic infiltrates are most frequently described in spleen, liver and lymph node, while pts with MCL usually lack skin lesions. Other organs that are rarely involved included kidneys, lungs, heart, tonsils and gastric mucosa [2, 3, 6]. Our results are very close to these reported in literature about involved organs but in our population, six pts had cutaneous lesions positive at biopsy for MC skin infiltrations. At diagnosis, five pts had splenomegaly with a median spleen diameter value of 16 cm (range 13–17); in two pts with ascites, liver biopsy revealed diffuse fibrosis and periportal infiltrates of MC. One of these pts had also pulmonary bilateral nodules, so

**Table 1** Clinical and biological characteristics of ten patients with mast cell leukemia

| Case | Sex/ Age (years) | WBC ($\times 10^9$/l) | HB (g/dl) | PLTS ($\times 10^9$/l) | Peripheral MC (% of leukocytes) | MC BM (%) | *c-kit* Mutation | Cytogenetic analysis | MC immunophenotype | Involved organ (other than BM) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F/45 | 5.13 | 8 | 190 | 9 | 90 | + | Normal caryotype | CD2, CD25, CD117/kit, CD9, CD45, CD33, CD4, CD84 | Cardiovascular system, spleen |
| 2 | M/74 | 12.80 | 11 | 67 | 8 | 88 | n.s. | 46 xy/46 xy del 5q- | CD2, CD25 | Spleen, liver, skin, lymph nodes |
| 3 | F/43 | 3.00 | 8 | 33 | 19 | 50 | + | Normal caryotype | CD2, CD25, CD117/kit | Cardiovascular system, spleen, liver, skeletal system |
| 4 | F/56 | 8.50 | 11 | 185 | 17 | 90 | + | Normal caryotype | CD2, CD25, CD117/kit | Cardiovascular system, skin, gastrointestinal tract |
| 5 | F/55 | 12.00 | 11 | 184 | 31 | 90 | − | Normal caryotype | CD2, CD25 | Spleen, skin, cardiovascular system |
| 6 | F/62 | 10.00 | 10 | 210 | 2 | 70 | + | Normal caryotype | CD2, CD25 | Cardiovascular system, spleen, liver, |
| 7 | F/60 | 5.60 | 11 | 80 | 1 | 30 | + | Normal caryotype | CD68, CD117/kit | Cardiovascular system, liver, lymph nodes, spleen, skin |
| 8 | F/62 | 5.40 | 8 | 158 | 9 | 30 | n.s. | Normal caryotype | CD2, CD25, CD117/kit | Skin |
| 9 | M/56 | 12.18 | 10 | 148 | 1 | 90 | − | Normal caryotype | CD25, CD117/kit | Cardiovascular system, liver, spleen, skeletal system |
| 10 | M/56 | 6.09 | 10 | 27 | 1 | 40 | + | Normal caryotype | CD2, CD25, CD117/kit | Skin, skeletal system |

*MC* Mast cells, *BM* bone marrow, *n.s.* not stated

**Table 2** Symptoms and treatments of ten patients with mast cell leukemia

| Case | Symptoms/Signs | Treatment | | | | | | Survival |
|---|---|---|---|---|---|---|---|---|
| | | First line | Outcome | Second line | Outcome | Third line | Outcome | |
| 1 | Headache, night sweats/ Weight loss, flushing, syncope, tachycardia, splenomegaly | Imatinib | NR | 2-CdA | Transient RP, progression after 8 months | Allogeneic HSCT | CR | Dead at 23 months in CR for accidental trauma |
| 2 | Fatigue/ Lymphoadenopathies, splenomegaly, hepatomegaly, cutaneous lesions | 2-CdA | Transient PR, progression after 7 months | Imatinib | NR | | | Alive at 48 months |
| 3 | Abdominal pain, fatigue, diarrhea, nausea/Weight loss, flushing, syncope, tachycardia, splenomegaly, fever, ascites, hepatomegaly, several radiographic lytic bone lesions | Idarubicin/ Cytosine arabinoside | NR | | | | | Dead at 2 months for progression of disease |
| 4 | Abdominal pain, fatigue, pruritus, nausea/ Tachycardia, fever, peptic ulcer disease, cutaneous lesions | α-Interferon | PR | | | | | Alive at 8 months |
| 5 | Fatigue, pruritus/Weight loss, flushing, hypotensive shock, splenomegaly, cutaneous lesions | Hydroxyurea | NR | Steroids | PR | | | Alive at 22 months |
| 6 | Abdominal pain, fatigue, diarrhea, nausea, pruritus, headache/ Weight loss, hypotensive shock, tachycardia, splenomegaly, hepatomegaly, | Steroids | NR | | | | | Alive at 3 months |
| 7 | Headache, pruritus/ Tachycardia, ascites, lymphoadenopathies, splenomegaly, hepatomegaly, cutaneous lesions | Imatinib | PR | | | | | Alive at 48 months |
| 8 | Pruritus, headache, fatigue/Cutaneous lesions | α-Interferon | NR | | | | | Alive at 98 months |
| 9 | Pruritus/Flushing, ascites, splenomegaly, hepatomegaly, radiographic bone lesions | Imatinib | Transient PR, progression after 3 months | Etoposide/ idarubicin/ tioguanine | NR | Hydroxyurea | PR, progression after 19 months | Dead at 29 months for progression of disease |
| 10 | Bone pain, pruritus/ Cutaneous lesions, radiographic bone lesions and vertebral pathologic fracture | α-Interferon | NR | Imatinib | NR | | | Alive at 24 months |

*CR* Complete response, *PR* partial response, *NR* no response

he underwent lung biopsy and broncoscopy with cytological exam of broncho-alveolar lavage fluid, which was positive for the presence of 9.5% of cells morphologically compatible with MC (CD117+, CD11b+, CD33+, CD2+, CD25+). In two pts, radiographic studies revealed abdominal lymphoadenopathy, while in the other three skeletal lesions were found.

So far, a widely accepted therapy is not known for MCL because of the low number of pts and lack of suitable models of this disease.

In our study, treatments were heterogeneous, and pts received different lines of therapy for the failure of the previous one: tyrosine-kinase inhibitor (Imatinib at dose of 400 mg/day), α-Interferon (3 MU/day×3/week), 2-CdA (0.14 mg/kg), conventional cytoriductive treatments, steroid therapy; one pt underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT).

As for the outcome, we reached poor results, and, in fact, we obtained only one complete response (CR) in the pt that received allo-HSCT after the failure of the previous two lines of treatments. Regarding the other therapeutic approach used, we obtained two partial responses (PR) among pts treated with Imatinib (two of five), both of them negative for *c-kit* D816V mutation, and other five PR after other drugs (two with 2-CdA, one with α-Interferon, one steroids and one Hydroxyurea, respectively). All these last pts relapsed after a median period of 10 months (range 3–19). The pts resulted refractory to the other therapies.

Two pts died for progression of disease, respectively, at 2 and 29 months from diagnosis; another pt in CR of disease died for accidental causes at 23 months from diagnosis and seven from CR. In contrast to other reported studies in the literature [7] in which most pts survive less than 1 year, in our study seven pts were alive at the last follow-up, with a median OS of 24 months (range 3–98), but in all cases with active disease.

Effective treatment is not yet available for pts with MCL that show no response or little remissions to conventional cytostatic drugs or aggressive polychemotherapy regimens, similar to those used to treat high-risk acute myeloid leukemia [2, 6, 7]. Furthermore, pts achieve only short-term remissions using interferon, steroid therapy or 2-CdA, and clinical studies showed failure of the tyrosine-kinase inhibitor imatinib in pts with D816V *c-kit* mutation [8]. If a bone marrow donor is available, allo-HSCT may be considered as a possible therapeutic approach, and in response pts can be evaluated for the possibility of combining HSCT with target therapy, α-Interferon or other experimental drugs in conditioning or maintenance treatment [9]. However, more data are needed to find new and successful therapeutic strategies.

## References


1. Valent P, Horny H-P, Escribano L, Longley BJ, Li CY, Scwhartz LB, Marone G, Nunez R, Akin C, Sotlar K, Sperr WR, Wolff K, Brunning RD, Parwaresch RM, Austen KF, Lennert K, Metcalfe DD, Vardiman JW, Bennett JM (2001) Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 25:603–625
2. Valent P, Akin C, Sperr WR, Horny HP, Arock M, Lechner K, Bennett JM, Metcalfe DD (2003) Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Haematol 122:695–717
3. Horny HP, Sotlar K, Valent P (2007) Mastocytosis: state of the art. Pathobiology 74(2):121–132
4. Valent P, Horny HP, Li CY, Longley JB, Metcalfe DD, Parwaresch RM, Bennett J (2001) Mastocytosis (mast cell disease). In: Jaffe ES, Harris NL, Stein H, Vardman J (eds) World Health Organization (WHO) classification of tumours. Pathology and genetics. Tumours of haematopoietic and lymphoid tissue 1. WHO, Geneva, pp 291–302
5. Valent P, Akin C, Sperr WR, Escribano L, Arock M, Horny HP, Bennet JM, Metcalfe DD (2003) Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. Leuk Res 27:635–641
6. Noack F, Sotlar K, Notter M, Thiel E, Valent P, Horny HP (2004) Aleukemic mast cell leukemia with abnormal immunophenotype and c-kit mutation D816V. Leuk Lymphoma 45(11):2295–2302
7. Hennessy B, Giles F, Cortes J, O'brien S, Ferrajoli A, Ossa G, Garcia-Manero G, Faderl S, Kantarjian H, Verstovsek S (2004) Management of patients with systemic mastocytosis: review of M. D. Anderson Cancer Center experience. Am J Hematol 77:209–214
8. Pardanani A, Elliott M, Reeder T, Li CY, Baxter EJ, Cross NC, Tefferi A (2003) Imatinib for systemic mast-cell disease. Lancet 362(9383):535–536
9. Spyridonidis A, Thomas AK, Bertz H, Zeiser R, Schimitt-Graff A, Lindemann A, Waller CF, Finke J (2004) Evidence for a graft-versus-mast-cell effect after allogeneic bone marrow transplantation. Bone Marrow Transplant 34(6):515–519