

Review Article

Granulocytic sarcoma: a systematic review

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Abstract: Granulocytic sarcoma also called myeloid sarcoma is an extramedullary tumor of immature granulocytic cells. It is a rare entity, and mostly accompanied by acute myeloid leukemia. It is observed during the course of myeloproliferative disorders especially in chronic myeloid leukemia and myelodysplastic syndromes. In some rare circumstances, it is detected before clinical signs of leukemia or other diseases. When the bone marrow biopsy reveals no other hematologic malignancies, the granulocytic sarcoma is described as nonleukemic, primary or isolated. It is observed at any part of the body but the most common locations are soft tissues, bone, peritoneum and lymph nodes. Presenting signs or symptoms are mainly due to mass effect of the tumor and dysfunction of the organ, or the tissue that is affected. The diagnosis is performed by biopsy of the tumor. The tumor consists of immature granulocytic cells, which could be documented by H&E, immunohistochemistry, and flow cytometric methods. Fluorescence in-situ hybridization and molecular analysis are also performed. The optimal time and type of treatment is not clear. Surgery could be an option especially for tumors, which cause organ dysfunction and/or obstruction. Systemic treatment should be considered in all patients because without systemic treatment, relapses and progression to acute myeloid leukemia is the ultimate fate of the disease in many cases. Cytarabine-containing remission-induction chemotherapies have been the most applied therapeutic strategies, but it is not clear whether the consolidation therapies are required or not, and what kind of regimens are appropriate. The role of hematopoietic stem cell transplantation (HSC) as a consolidation regimen is not clear, but, after the relapse of the disease with or without bone marrow involvement, HSC transplantation should be considered in suitable patients after the reinduction performed by AML chemotherapies. There is only limited data about the role of radiotherapy in these patients. It could be used in patients with relapsed disease, organ dysfunction which should be quickly relieved and inadequate response to chemotherapy. The effect of radiotherapy on overall survival is not known. New prospective studies and clinical trials are needed to generate guidelines for the treatment of primary granulocytic sarcomas.

Keywords: Granulocytic sarcoma, treatment, chemotherapy, leukemia

Introduction

Myeloid sarcoma (MS), or granulocytic sarcoma, is a tumoral lesion consists of immature cells of granulocytic series. It is also known as chloroma due to its green color attributed to the enzyme myeloperoxidase (MPO). It has been identified as an extramedullary presentation of acute leukemias especially in acute myeloid leukemia. It was shown to be detected simultaneously with the disease or during the course of the disease, and also at relapses after allogeneic stem cell transplantation. Less commonly, it has been observed during the course of myelodysplastic syndrome, chronic myeloid leukemia and other myeloproliferative diseases [1-9].

MS was shown to precede acute myeloid leukemia at which the bone marrow aspiration and biopsy reveal no hematological disease. This type of MS is called isolated, primary or nonleukemic MS. It is a rare disease with an incidence of 2/1.000.000 in adults. In the literature, there are only case reports and some small series most of which are retrospective studies. It has been identified to be solitary or multiple [10].

MS occurs at any age both in pediatric and elderly patients [10], and at any site of the body but the most common locations are soft tissues, bone, peritoneum, lymph nodes, and gastrointestinal system [7, 10, 11]. Other sites that are presented in the literature are the genitouri-

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nary system of males and females and the central nervous system [3, 12-17]. Since the locations are diverse, clinical presentation of the disease is also diverse with signs and symptoms determined by the size and localization of the tumor [11].

Diagnosis

Diagnosis of MS with known AML or other hematologic malignancies is relatively easy but the differential diagnosis of primary MS is relatively difficult for a pathologist. The rate of misdiagnosis is 75% in a historical study, and the most frequent misdiagnosis is large cell lymphoma [18]. In recent studies, the rate of misdiagnosis has been found to be lower with a range of 25-47% [19, 20]. The patients were mostly mistaken for malignant lymphoproliferative disorders. The misdiagnoses are non-Hodgkin lymphoma, histiocytic lymphoma, thymoma, myeloma, eosinophilic sarcoma, extramedullary hematopoesis, mucosa associated lymphoid tissue, Ewing sarcoma and carcinoma, and they could not be corrected until acute leukemia was suspected by bone marrow aspiration and biopsy or peripheral blood smears [19, 20]. Although the fine needle aspiration is used for diagnosis in the literature [21], tissue biopsy is the preferred method [11]. The morphologic appearance on H&E varies according to differentiation of the cells. It mostly consists of infiltration by myeloblasts. It is recommended to send the specimen to immunohistochemistry, flow cytometry, fluorescence in situ hybridization, and molecular analysis. Following the diagnosis of MS, bone marrow biopsy and aspiration should be performed to rule out other hematological malignancies [11]. Fine needle aspiration should be reserved for tumors in which tissue biopsy is not suitable.

Imaging tests

According to the localization of the tumor, magnetic resonance or computed tomography is performed. These techniques differentiate MS from abscess and hematomas especially in patients with AML [22]. Stölzel *et al* have also shown that FDG-PET CT is an option to document the localization, and size of the tumor, and to detect multiple lesions in nonleukemic MS and MS with AML [23]. PET CT is mostly suggested for planning of the radiation therapy and monitoring the treatment response [11].

Especially in patients with CNS, spinal and musculoskeletal lesions, usage of MRI with contrast material would be preferred [24, 25].

Prognosis

The prognosis of isolated MS is not well examined in large prospective studies but it has a poor prognosis. In some series with subgroup analysis of isolated MS performed in children, it was demonstrated that it had a better prognosis than children with AML, without MS and patients concomitant with AML [26]. Tsimberidou *et al* have demonstrated that isolated MS patients with chromosome 8 abnormalities had a worse prognosis and intensive chemotherapies were needed in this group [12].

Treatment

Since primary MS is a rare entity, there are not large prospective randomized studies which would document optimal treatment. Data about the treatment options of the disease comes from case reports and small case series most of which are retrospective studies. The treatment depends on the localization of the disease, whether it is an initial diagnosis or at relapse, the performance status and the age of the patient. In some historical studies, Meis *et al* [18] have reported 16 granulocytic sarcoma patients without evidence of leukemia, and have pointed out that 4 of those 16 (25%) patients did not develop acute leukemia during the follow up period of 3.5-16 years, but they have not identified any prognostic factors about progressing to acute leukemia. Tsimberidou *et al* demonstrated that isolated MS had a better event free survival in patients treated with cytarabine containing regimens [27]. In the literature, since there is a high rate for progression to acute leukemia especially in patients who are treated with localized methods (88-100%), systemic treatment is recommended to all patients with isolated MS [11, 25].

The type and time of the systemic treatment

Although the optimal time and type of the chemotherapy is not clear in isolated MS patients, chemotherapy regimens similar to the regimens used in AML remission induction treatment are mostly used. Tsimberidou *et al* [12] showed that AML patients treated with chemotherapy (idarubicine and ara - C; fludarabine,

ara - C, idarabucin and G - CSF [FLAG]; cyclophosphamide, cytarabine, topotecan and G - CSF [CAT - G]; daunorubicin and ara - C) with or without radiotherapy had 65% complete remission and the median survival was 20 months. Other studies also demonstrated the effectiveness of systemic chemotherapy in primary MS patients [20, 27, 28]. Imrie *et al* [28] documented that systemic chemotherapy has decreased the rate of progression to acute leukemia (41% versus 71% $p = 0.001$) and increased the survival. The period of progression to acute leukemia is longer in patients treated systemically than in patients treated only with local approaches like surgery or radiotherapy [20]. Under the light of these studies, treatment with systemic chemotherapies should be initiated as soon as the diagnosis is confirmed [11, 27, 29]. It is documented in the literature that the treatment of MS should also be initiated as soon as the diagnosis is confirmed in the pediatric group [30].

Upon consideration of the type of chemotherapeutic agents, there are very limited data analyzing the different agents in primary MS patients. In a retrospective study, in patients treated with chemotherapeutic agents containing cytosine arabinoside and anthracycline, which is accepted as the treatment of acute myeloid leukemia; the period of progression to acute leukemia was significantly longer than in patients who were treated with chemotherapies that were used mostly in patients with lymphomas [20].

So immediate systemic treatment with agents used in patients with acute myeloid leukemia should be given to the patients with primary MS [11, 29].

Local approaches in primary MS patients

Radiotherapy (RT)

In retrospective groups, it was shown that patients treated only with radiotherapy had a high rate of progression to AML after a short nonleukemic period [20]. It could also be used as a consolidation therapy after systemic chemotherapy [11] while considering the possible toxicities due to the localization of the tumor. Tsimberidou *et al* demonstrated that the failure free survival in 21 patients with nonleukemic granulocytic sarcoma was lower with the com-

ination treatment of chemoradiotherapy [12]. In another retrospective case, with a group of 90 patients, the local radiotherapy had no effect on survival in multivariate analyses [28, 31].

In conclusion, RT without systemic treatment is not an optimal therapy for primary MS patients. It could be used in conjunction with systemic therapies, primarily in patients who need a rapid relief of symptoms, or it could also be used as a consolidation therapy. In patients with CNS involvement, radiation therapy should be used in combination with systemic therapies.

Surgery

Most of the patients, who undergo surgery, almost always relapse or progress to AML, and die. The incidence of AML or extramedullary relapse was significantly higher in patients who were treated with surgery only [19]. It was also demonstrated by Yamauchi *et al* that the time interval to progression to AML was higher in patients who did not receive systemic therapy [20]. Most of the patients (81%) who did not receive systemic treatment were shown to progress to AML in the first 11 months. A non-leukemic period longer than 2 months was observed in 19% of patients who received systemic treatment, and in only 5% of patients who were not treated systemically [20]. Under these circumstances, only surgery is not an effective treatment strategy for primary MS, and surgery should be considered before the systemic treatment in acute situations in which rapid debulking and symptomatic relief is needed [11]. It could also be used to confirm the diagnosis in rare cases.

Bone marrow transplantation

There are no prospective studies about hematopoietic stem cell transplantation (HCST) in isolated MS patients. The data about HSCT comes only from retrospective small groups mostly MS concomitant with AML. One of the largest groups consisted of 99 myeloid sarcoma patients with 30 isolated MS patients. In this study, the subgroup analysis of isolated MS patients was documented, and it was found that allogeneic stem cell transplantation was an efficient treatment modality with a non-relapsing mortality rate of 17%. Nearly half of

the patients (47%) in this study got transplantation in the first remission. The 5-year overall survival was 33% and leukemia free survival was 30%, and there was no statistically significant difference between the isolated MS and leukemic MS patients. Other studies consisted of both isolated MS and MS with AML. It was concluded that HSCT should be considered as a first line effective therapeutic option with longer overall survivals [19, 25, 32, 33].

Under the light of these data, HSCT would be considered in patients with isolated MS especially in relapsed patients and in patients who are in their first remission [11].

Targeted therapies

There is no targeted therapy for patients with MS but new agents such as FLT 3 inhibitors, farnesyl-transferase inhibitors and, histone deacetylase inhibitors studied in patients with AML could be considered as an option for MS patients [25].

Therapies in relapsed or refractory disease

There is very limited data about relapsed patients. Relapsed or refractory disease is observed with or without bone marrow involvement. In these patients, reinduction chemotherapies should be considered concomitant with HSCT. If the relapse occurs after HSCT, donor lymphocyte infusion, tapering of the immunosuppression treatment and RT would be an option. If there is concomitant bone marrow involvement, the patients are treated as relapsed AML with chemotherapy reinduction and HSCT. RT could be used as a local control of the disease [11]. These patients should be considered to enroll a clinical trial.

Consolidation treatment in remission after the first line chemotherapy is not well studied. Some authors only recommend radiotherapy as although others conclude that consolidation with HSCT has a longer survival [11, 34].

Conclusion

Isolated MS is a rare tumor that consists of immature granulocytic cells. It is detected at any part of the body. The optimal treatment of the disease is not clear since there is not enough data and large prospective studies in the literature. Systemic chemotherapies used

in AML remission induction treatment are mostly suggested therapy with or without radiotherapy. HSCT should also be considered in relapsed or refractory patients after reinduction and used as a consolidation treatment in suitable patients. New large prospective studies and new agents are needed for the treatment of isolated AML patients.

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Disclosure of conflict of interest

None.

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