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Hematology and Disorders
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ISSN: 2836-3582 RESEARCH ARTICLE

Myeloid Sarcoma: Current Approach and Treatment Strategies

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Received Date: 27 October 2022; **Accepted Date:** 14 November 2022; **Published date:** 12 December 2022.

Citation: Govind R.Patel, Aggarwal.S.(2022). Myeloid Sarcoma: Current Approach and Treatment Strategies. Journal of Hematology and Disorders. 1(1). 10.58489/JHD.002.

Abstract

Myeloid sarcoma (MS) is a rare extramedullary tumor of immature myeloid cells with associated tissue damage. Although MS can manifest as isolated form without blood and marrow involvement, in the majority of the cases it is associated with acute myeloid leukemia (AML). Rarely, it may present in other myeloid disorders. It should, therefore, be considered in a differential diagnosis of any atypical soft tissue mass. MS can develop at any site, resulting in varied clinical manifestati ons. Identification and diagnosis of MS is highly challenging and depends on a high index of suspicion as well as on imaging, histopathology, immunophenotyping, and genetic analyses. Owing to the lack of prospective clinical trials, there is not enough data in the field to develop a consensus therapeutic regimen for MS. Majority of the patients with MS, including isolated MS, respond to upfront systemic chemotherapy using AML-like regimens that should be commenced early. Surgical resection and/or radiation therapy can be employed for symptomatic lesions or tumors causing local organ dysfunction or obstruction. Allogeneic hematopoietic stem cell transplantation has demonstrated promising results as consolidation therapy after complete remission with induction chemotherapy. Recent development in sequencing analysis has provided significant insights into the development of novel targeted therapies. At present, there are no validated prognostic factors for MS which can help in risk stratification of patients and treatment planning. As there is limited knowledge regarding the clinical approach and management strategies of MS, this review aims to update current knowledge about MS.

Keywords: *Myeloid sarcoma, Granulocytic sarcoma, Acute myeloid leukemia, Extramedullary, Current approach.*

Abbreviations: *MS, myeloid sarcoma; MPO, myeloperoxidase; WHO, world health organization; BM, bone marrow; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; allo-HSCT, allogeneic HSCT; FAB, French-American-British; DLI, donor lymphocyte infusion; MMP, matrix metalloproteinase; EZH2, enhancer of Zeste 2; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; 18F-FDG, 18F-fluorodeoxygenase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; CBF, Core binding factor; MLL, mixed lineage leukemia gene; NPM1, nucleophosmin 1; FLT3, fms-like tyrosine kinase 3; ITD, internal tandem duplication; RT, radiation therapy; HMAs, hypomethylating agents; CR, complete remission; DFS, disease-free survival; OS, overall survival; haplo-HSCT, haploidentical HSCT; auto-HSCT, autologous HSCT; GVHD, graft-versus-host disease; NGS, next-generation sequencing; TKIs, tyrosine kinase inhibitors; GVL, graft-versus-leukemia.*

Introduction

Myeloid sarcoma (MS), also known as chloroma, granulocytic sarcoma, myeloblastoma, myelocytoma, chloroleukemia or extramedullary myeloid cell tumor, is a rare, extramedullary malignant tumor formed by an abnormal proliferation of immature precursors of myeloid cells that disrupts the normal architecture of the tissue in which it is found [1]. It was originally described in 1811 by a British physician, Alan Burns, and later investigated in 1853 by King who coined the term, “chloroma” (Greek, Chloros, meaning green) as it appears green in color probably due to the presence of intracellular enzyme myeloperoxidase (MPO) [2,3]. In 1966, Rappaport renamed it as “granulocytic sarcoma”. In 2002, the World Health Organization

(WHO) declared the name “myeloid sarcoma” that seems to be the most frequently used term, since around 30% of tumors do not show MPO positivity [1,4].

MS may occur as a de novo isolated or primary non-leukemic form without blood and/or bone marrow (BM) involvement, and in the absence of any history of myeloid neoplasia, may manifest with concurrent acute myeloid leukemia (AML), may present as extramedullary relapse of AML, especially following hematopoietic stem cell transplant (HSCT), or less frequently, may occur in chronic myeloid leukemia with impending blast crisis or as the progressive form of non-leukemic conditions such as myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or MDS/MPN [2,5-11]. MS is classified by the WHO as one of the major subgroups of AML and related neoplasms with a unique clinical presentation of any subtype of AML [2,12]. As the literature about MS is primarily restricted to small retrospective studies, case series and case reports, there is limited knowledge regarding the clinical presentation, diagnostic approach, prognostic factors and management strategies of MS. Therefore, the aim of this review is to provide updated clinical knowledge about MS, focusing mainly on isolated MS and MS occurring concurrently with AML.

Epidemiology

MS is indeed a rare disease; the exact incidence and the prevalence of MS are not well described owing to a limited number of prospective studies. It affects both genders with a slight male predominance. While MS may develop at any age, children seem to be affected more than adults as nearly 60% of cases of MS are below 15 years of age with a median age of 7 years [9,13,14]. Isolated MS is relatively a rare manifestation with an incidence of 2 cases per million adults. In patients with AML, MS occurs in approximately 2.5% to 9.1% of patients across genders and all age groups [6,9,15-17]. In nearly 35 % of cases, MS precedes diagnosis of AML. However, it may undergo a leukemic transformation in an average interval of 10 month [8]. MS occurs concomitantly with AML in 15–35% of cases, while it can appear after the diagnosis of AML in 50% of cases as a complication of AML or as a relapse during remission. The incidence of MS after allogeneic HSCT (allo-HSCT), manifesting as an isolated disease or accompanying blood and BM relapse, has been reported to be 0.2%-1.3% [18,19]. Certain types of AML predispose the individual to develop MS which includes M4 and M5 French-American-British (FAB) subclasses of AML. Other risk factors include high peripheral total white cell counts, chromosomal abnormalities t (8;21) or inv (16), and myeloblasts expressing T cell markers.

Although uncommon, the incidence of MS is increasing. This is partly due to a reported increase in the likelihood of extramedullary relapse in AML after allo-HSCT or due to the increased longevity of patients since the emergence of new treatment options for leukemia such as allo-HSCT with repeated donor lymphocyte infusion (DLI), and therapy with novel targeted agents, like small molecule inhibitors, histone deacetylase inhibitors, DNA methyltransferase inhibitors, and nucleoside analogues [5].

Pathogenesis

The exact mechanism underlying the pathogenesis of MS is not clear. It can be argued that extramedullary tissues have reduced immune surveillance that facilitates cancer immune evasion. Extramedullary infiltration in MS may result from the presence of an aberrant homing signal for the blast cells that enables them to re-localize to secondary sites precluding the more common BM localization. These blasts may represent a subclone of an original AML clone in cases of concurrent presentation or in the relapse condition. The different chemokine receptors implicated in the homing and retention of AML blasts in extramedullary sites include CCR5, CXCR4, CXCR7, and CX3CR1 [20]. The specific interactions between the matrix metalloproteinase (MMP)-9 and leukocyte surface beta (2) integrin along with some unidentified proteins, termed the complex “invadosome” has also been suggested as a major factor for the invasion and migration of AML-derived blast cells into non-myeloid extramedullary regions [3]. The role of MMPs in extramedullary blast penetration and migration is further supported by another study [21]. Recently, a correlation between increased expression of enhancer of Zeste 2 (EZH2) and extramedullary infiltration of AML has been reported [22].

Clinical presentation

The clinical presentation of MS is diverse owing to variation in the location and size of lesions. Studies to establish a predilection of MS for various sites are lacking. It is thought to originate in the BM, the cells being spread through the Haversian canals to penetrate the subperiosteum to form soft tissue masses into extramedullary regions which explains its typical location near bone structures. It can involve any site of the body. The most commonly affected sites, as reported in the literature, include the lymph

nodes, skin, soft tissues, bone, periosteum, testes, gastrointestinal tract, and retroperitoneum; however, it can also occur in central nervous system (CNS), oral and nasal mucosa, breasts, genitourinary tract, chest wall, and pleura [6,9,13,14,16,17,23,24]. In children with newly diagnosed AML, the development of MS is most common in the skin (54%), followed by orbital region [6,16,17,25]. The size of MS lesions at diagnosis is highly variable ranging from 2 to 20 cm.

Although MS is asymptomatic in majority of cases, it has various clinical manifestations determined by its size and specific location. When MS presents as an isolated finding, this may mimic inflammatory/infective or lymphoproliferative diseases. The most common signs and symptoms associated with MS are usually occurring as a result of a tumor mass effect or local organ dysfunction accompanied by other symptoms such as pains, bleeding, fever and fatigue [2,9,13].

Diagnosis

Timely diagnosis of MS is warranted as the early diagnosis of MS has a significant impact on the treatment outcomes due to its high responsiveness to systemic chemotherapy and local irradiation. As there is no specific diagnostic test for MS, its diagnosis is based on a combination of clinical features, radiological investigations, and in most cases, tissue biopsy. The clinical diagnosis of MS is highly challenging as MS is asymptomatic and does not cause any specific symptoms in majority of cases. Any atypical soft tissue mass, at any site, particularly but not exclusively where there is a history of myeloid neoplasia should raise the suspicion of MS. The diagnosis of MS in patients with concomitant or pre-existing AML is relatively easier than isolated MS.

Imaging

Given the wide variation in sites of involvement of MS, imaging is required for the early detection of tumors. Traditional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) as well as positron emission tomography (PET) scan are helpful in identifying MS [26,27]. As MS often appears as a soft tissue mass, best suited imaging technique for its detection is CT. However, CT findings may be variable since MS can be circumscribed or diffusely infiltrating. Lesions of MS are frequently hypodense with mild enhancement. Sometimes it can present as heterogeneous enhancing with non-enhancing areas which represent necrosis and sign of rapid growth. On MRI, it is isointense or hypointense on T1 weighted and mildly hyperintense on T2 weighted images. MRI (gadolinium enhanced) is specifically useful for MS involving CNS. It can also be used in follow-up imaging because the radiation concerns are little. Nuclear imaging such as 18F-fluorodeoxygenase (18F-FDG) PET/CT and gallium 67 shows avid uptake by MS which can be used to decipher the multiplicity as well as to monitor treatment response. 18F-FDG PET/CT is able to identify new sites of MS, which is not identified by traditional imaging techniques [10]. In addition, it is also very important in radiotherapy planning. 18F-FDG PET/CT has become an essential tool for the detection of extramedullary disease over the last few decades [10,27,28,29]. However, it is not sensitive enough to detect MS lesions in skin, meninges and mucus membranes. Also, there is an increased incidence of false-positive signals associated with 18F-FDG PET/CT, specifically in brain and kidney that have high basal glucose metabolism [11].

Morphology and immunophenotyping

Every attempt should be made to obtain a tissue sample to confirm the diagnosis if the risk of biopsy is reasonable. MS often poses a serious diagnostic challenge to a pathologist. MS is defined by the WHO as a tumor mass consisting of myeloid blasts with or without maturation occurring at an anatomic site other than the BM causing effacement of local tissue architecture [12]. In order to accurately diagnose MS, histological examination and immunophenotypic analyses are needed. When immunophenotyping is not used, MS is often misdiagnosed as several malignant and non-malignant masses such as large cell lymphoma, small round cell tumors (neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and medulloblastoma), undifferentiated cancer, malignant melanoma, extramedullary hematopoiesis or inflammation [8,23,24].

The histological appearance of MS typically consists of a diffuse and infiltrative population of myeloblasts and granulocytic cells at different stages of maturation. The infiltrating malignant cells are typically large with abundant cytoplasm and irregular large nuclei. Based on the predominant cell types in the tumors, MS is classified into granulocytic, monoblastic and myelomonocytic subtypes. Additionally, MS is further subdivided into immature, mature and blastic types based on the maturity of the cells [17]. Importantly, the malignant cell lineage should be consistent with the underlying myeloid neoplasia. Cytochemical stainings on imprints may confirm the myeloid cell lineage and differentiate granulocytic and monoblastic forms. According to the WHO 2016 classification, cytochemical stains should

include MPO, chloroacetate esterase (positive in granulocytic MS) and non-specific esterase (positive in monoblastic MS) [12]. MPO staining is very often positive in the malignant cells of MS, which is a quick way for establishing the diagnosis and ruling out other tumors. Immunophenotying is crucial for the accurate diagnosis of MS which can be done either by flow cytometric analysis on cell suspensions derived from the tumor or, more commonly, by immunohistochemistry (IHC) on paraffin-embedded tissue sections. The most commonly expressed markers on IHC include CD68/KP1, MPO, CD117, CD99, CD 68/PG-M1, lysozyme, CD34, TdT, CD56, CD61, CD30, glycophorin A, and CD4. Flow cytometry shows CD13, CD33, CD117 and MPO as the most common positive markers in tumors with myeloid differentiation, and CD14, CD163 and CD11c with monoblastic differentiation [2,13]. B- and T-lineage markers, in particular CD20, CD45RO, CD79a and CD3, should be added to the panel in order to exclude the possibility of lymphoma [2]. In addition, once the extramedullary mass is established as MS, a BM aspirate and biopsy should also be performed and sent for identical studies. Constellations of cytochemical stains and immunophenotypic markers more precisely defining subtypes of MS are shown in Table 1.

Table 1: Common cytochemical stains and immunophenotypic markers in different subtypes of myeloid sarcoma

Subtypes	Cytochemical stains	Immunophenotypic markers
Granulocytic	Myeloperoxidase (MPO) and chloroacetate esterase	Myeloperoxidase (MPO),CD13,CD33, CD117, CD68 (detected by KP1 monoclonal antibody but not by PG-M1) and CD34
Myelomonocytic	MPO in distinct subpopulations	Homogeneous expression of CD68 (KP1), while CD68 (PG-M1) and MPO in distinct subpopulations
Monoblastic	Non-specific esterase	CD68 (PG-M1), CD14, lacking MPO, CD163 and CD11c

Abbreviations: MPO, myeloperoxidase; CD, cluster of differentiation

Cytogenetics and molecular abnormalities

A simple pathological diagnosis of MS is insufficient to risk stratify and formulate optimal treatment strategies in the modern era of targeted treatment. Therefore, an attempt should be made to define the chromosomal and molecular genetic abnormalities in patients with MS [5]. Conventional karyotyping, fluorescence in situ hybridization (FISH) and a sequencing (whole-genome, whole-exome, and RNA sequencing) based analysis should be employed in case of MS similar to AML.

Several chromosomal abnormalities have been reported in MS, with a wide variation in frequencies in different studies. An analysis has demonstrated cytogenetic abnormalities in more than 50% of MS patients [24]. Core binding factor (CBF) leukemias and AML with mixed lineage leukemia gene (MLL) rearrangements are most frequently reported associations with MS [30]. The translocation t (8;21) is the most commonly reported chromosomal abnormality (ranges from 3.3% to 43%) in MS, and is mainly associated with orbital MS in children [24,31,32]. The inv (16) is the next most frequent cytogenetic abnormality observed in MS, particularly in the abdomen and characterized by a microscopic appearance of plasmacytoid monocyte clusters [6,24,27,33]. Pileri et al showed the relative rarity of t (8,21) in adult MS patients, while trisomy 8, monosomy 7 and MLL rearrangements comprised the majority of the cases in these patients [24]. The prevalence of inv (16) was also not well documented in adult patients. Other reported chromosomal abnormalities in MS include t (9;11), del(16q), t (8;17), t (8;16), t (1;11), trisomy 11, trisomy 4, monosomy 16, del(5q), and del(20q). In addition, monosomy 5, 8 or 16 were also reported in isolated cases.

Studies conducted with small cohorts of patients with MS reported mutations in nucleophosmin 1(NPM1) and fms-like tyrosine kinase 3 (FLT3) genes. NPM1 mutations have been reported in 14% of MS patients. This variant of MS clinically presents similar to NPM1 positive AML and occurs primarily in M4 and M5 FAB subclasses of AML [34]. NPM1 mutated MS is also associated with the loss of CD34 expression and normal karyotype. FLT3 internal tandem duplication (FLT3-ITD) mutation have been reported in 33% of MS patients with concurrent AML [35]. In addition, sequencing analysis has identified mutations in several genes similar to AML such as KIT, TET2, EZH2, SF3B1 and ASXL1 in MS [36,37]. KIT is a common mutation in MS with t (8;21)-associated AML.

Treatment

Given the lack of prospective randomized controlled trials, there is no consensus on the best therapeutic regimen of MS, and its treatment strategies are limited. Management of MS depends on a number of factors, including size and location of tumor, its

relation to local structures, the timing of diagnosis of the extramedullary tumor in relation to de novo or relapsed disease, any prior treatment, age, and performance status. Based on the existing data, the best course of treatment for different variants of MS is systemic chemotherapy, in association with radiation therapy (RT), surgical resection and allo-HSCT depending on the BM involvement. In recent years, with the rapid development of cytogenetics and molecular biology, hypomethylating agents (HMAs), targeted therapy, and immunotherapy have been shown to be effective.

Systemic chemotherapy

Systemic chemotherapy represents the mainstay of treatment for both isolated MS and MS with concurrent AML, given the fact that even if there is no primary BM involvement, most (71%-100%) isolated MS patients treated with localized methods (surgery and/or radiotherapy) progress to AML [6,38]. Hence, chemotherapy should be commenced in all cases, including after complete resection of isolated MS. Chemotherapy includes both induction and consolidation phase. A variety of chemotherapy regimens are used in MS and generally follow the same protocol as AML, mainly including cytarabine (cytosine arabinoside) with fludarabine, idarubicin, or daunorubicin [28,39]. However, at present there is a lack of data to identify a specific chemotherapeutic regimen that is beneficial for MS. Nevertheless, existing data indicates cytarabine to be an essential drug in this regard [39]. In particular, conventional AML-type combination chemotherapy with cytarabine and daunorubicin has been demonstrated to achieve complete remission (CR) in 65% of MS patients [40]. In isolated MS patients treated with AML-based induction regimens, CR rates are comparable with AML without MS with similar prognostic features, and prolonged disease-free survival (DFS), from 3.5 to 16 years, has been reported [40]. Studies led by different groups have shown that standard AML therapy exhibits better overall survival (OS) in case of isolated MS [16]. Additionally, chemotherapy has also shown to be effective in retarding AML progression in isolated MS cases (71%) in both adult and pediatric population [39]. MS associated with other myeloid neoplasms also warrants systemic chemotherapy because it suggests leukemic transformation.

Local Therapy

Local therapy involves either surgical resection or RT or a combination. Although surgery or radiotherapy alone may play an important role in controlling the primary disease and relieving local compression symptoms without much toxicity, it cannot prevent or delay the progression of MS. Retrospective series have demonstrated that isolated MS treated with local therapy alone has a high rate of evolution into the systemic disease and AML with a short nonleukemic interval [4,15,39]. Yamauchi and Yasuda reported that 81% of patients treated with surgery alone progressed to AML within 11 months of diagnosis [39]. The role of radiotherapy is not well established for treatment of MS. Existing data suggest that RT alone may not be sufficient for complete eradication of MS. Bakst et al has shown that patients with isolated MS usually respond better to systemic chemotherapy compared to RT [38]. Additionally, there is no conclusive data showing that radiotherapy alone in MS can prevent progression to leukemia. As a consequence, RT is mostly given in combination with systemic chemotherapy to treat MS. Combined treatment with chemotherapy and radiotherapy had better survival than chemotherapy alone in isolated MS [40]. However, several study groups have not found any significant difference in outcome with or without radiotherapy [17,25]. If the MS persists after completion of induction chemotherapy, local treatment such as surgery and radiotherapy may be considered.

Hematopoietic stem cell transplantation

HSCT is another therapeutic option for MS patients [2]. There are no controlled trials evaluating the role of HSCT in patients with MS. However, reported data suggests an advantage of HSCT in isolated MS or MS with concomitant AML irrespective of age, gender, anatomic location, clinical presentation or cytogenetic status [2,6,17]. Given the encouraging results in form of better OS rate and improved adverse outcomes in MS from several retrospective studies in both adults and children [24,41,42,43], allo-HSCT can be considered as a first-line treatment option for consolidation therapy after induction of remission and as a salvage therapy in relapsed or refractory disease for patients with MS and concurrent marrow involvement after evaluation of other patient-related factors, including standard age and cytogenetic and molecular based risk profiling [2,4,6,24,43,44,45,46]. In addition, allo-HSCT has been shown to be beneficial in treating isolated MS [25,43,44]. Consequently, many clinicians considered allo-HSCT as a primary line of treatment following remission even in isolated MS patients.

Most of the studies involved either matched sibling donors or matched unrelated donors for allo-HSCT. Haploidentical HSCT (haplo-HSCT) can be considered in patients without a fully matched HLA

donor given the favorable results of haplo-HSCT in patients with MS in a study by Yu et al [47]. Transplant-related mortality and graft-versus-host disease (GVHD) may result from allo-HSCT, therefore autologous HSCT (auto-HSCT) has been proposed as an approach to achieve long-term survival in young, chemotherapy-sensitive, and minimal residual disease-negative patients with MS [48,49]. However, most of the data on auto-HSCT have been derived from case reports.

Targeted therapy

The recent development in next-generation sequencing (NGS) and other molecular techniques has provided significant insights into the pathogenicity of hematological malignancies, and thereby opportunities for highly targeted therapies. However, due to the rarity of the disease, and the previously limited access to genetic analysis, clinical trials for targeted therapies in MS are still lacking. Therefore, much of the available data relies on non-controlled anecdotal reports. Targeted therapy using a humanized anti-CD33 monoclonal antibody demonstrated encouraging results in patients with MS associated with CD33-positive AML [50,51]. MS patients with BCR-ABL1, FLT3-ITD and FIP1L1-PDGFRA mutations also showed favorable results with treatment by tyrosine kinase inhibitors (TKIs) [52,53]. TKIs can target the KIT mutation and KIT protein overexpression, thus improving the remission rate and reducing recurrence. In a recent study by Zhao et al, favorable outcomes have also been demonstrated in MS patients treated with a TKI combined with HSCT as well as with chemotherapy [54]. Furthermore, a patient with refractory MS also achieved complete remission with single-agent venetoclax [55].

Hypomethylating agents

In patients with MS, use of HMAs (decitabine and azacitidine) may be a treatment option. Several reports have shown that HMAs, through immunomodulatory effects, can be used alone [56] or in combination with chemotherapy [57], radiotherapy [58], and targeted therapy [59] to increase the antitumor effect in patients with MS. Furthermore, animal experiments and clinical observations have suggested that decitabine is safe and effective in treatment of MS associated with the TET2 mutation [37]. HMAs can be safely used in MS as maintenance therapy after allo-HSCT to prevent its recurrence and reduce GVHD [54]. HMAs can enhance the expression of NK cells and cytotoxic CD8+ T cells, and increase the immune recognition of donor-derived T cells to leukemic cells after HSCT [54]. HMAs also play a role in graft-versus-leukemia (GVL) reactions by upregulating the expression of silenced WT1 tumor antigen and HLA-II molecules through demethylation. Some success has been reported in patients with refractory/relapsed MS [54].

Relapsed MS

Recurrence after MS remission remains a clinically challenging situation. MS is usually sensitive to chemotherapy or irradiation and resolve fully within 3 months, though in about 23% of the patients, it recurs. The reported recurrence rate is 50% after HSCT in MS [45]. Isolated MS at relapse is rare and considered a systemic disease despite normal blood and marrow findings as it often heralds systemic relapse. The median interval until marrow relapse in this setting is approximately 7 months [60]. On average, the median survival after diagnosis of MS is 7.5 months. The underlying mechanism involved in MS relapse, especially after allo-HSCT, is immune escape. MS may serve as a sanctuary site for future leukemic relapse due the fact that MS reflects a state of reduced immune surveillance and less effective GVL reactions in a patient at diagnosis or following HSCT [27]. Downregulation of HLA-II expression caused by hypermethylation of promoter class II transactivator might be a mechanism responsible for the immune escape of leukemic cells after HSCT akin to AML [54]. Studies have suggested that reduced-intensity conditioning, compared to myeloablative conditioning, may increase the risk of extramedullary recurrence after allo-HSCT [54,61].

There are few therapeutic options available for relapsed MS, especially after HSCT. Therefore, effective prevention of recurrence, especially after HSCT, is the key to improving the outcomes of MS. Methods such as immunosuppression reduction, intensive chemotherapy, DLI, and secondary HSCT have limited efficacy and an increased incidence of adverse reactions. In recent years, HMAs, molecularly targeted drugs, and cellular immunotherapy have gradually shown good efficacy in preventing relapse. Treatment options for patients who have relapsed after chemotherapy alone include reinduction chemotherapy and RT. Patients with a relapsed MS respond poorly to chemotherapy than those who present with a newly diagnosed MS. As there is no standard chemotherapy regimen for relapsed MS, a regimen similar to that used in relapsed AML is selected for its treatment. HSCT is often recommended, although its potential benefits in this setting are unclear. HMAs are equally effective

and safe in the treatment of extramedullary recurrent MS after HSCT [62,63].

A summary of preferred treatment strategies in MS is depicted in Table 2

Table 2: A summary of preferred treatment strategies in myeloid sarcoma

Timing of presentation	Extent of involvement and setting	Treatment strategies
de novo	*Isolated MS*	*AML-type chemotherapy with consideration of RT as consolidation*
	MS with concurrent marrow involvement	*AML-type chemotherapy with consideration of HSCT as consolidation; RT if MS persists after induction chemotherapy*
Relapse	***Isolated MS***	
	After chemotherapy	*Reinduction AML-type chemotherapy with consideration of HSCT consolidation; RT if MS persists after reinduction chemotherapy*
	After HSCT	*Immunosuppression reduction, AML-type intensive chemotherapy, DLI, secondary HSCT, RT, and/or clinical trial*
	MS with concurrent marrow involvement	
	After chemotherapy	*Reinduction AML-type chemotherapy with consideration of HSCT as consolidation, RT if MS persists after reinduction chemotherapy, and/or clinical trial*
	After HSCT	*Immunosuppression reduction, AML-type intensive chemotherapy, DLI, secondary HSCT, HMAs, RT, and/or clinical trial*

Abbreviations

MS, myeloid sarcoma; AML, acute myeloid leukemia; RT, radiation therapy; HSCT, hematopoietic stem cell transplantation; DLI, donor lymphocyte infusion; HMAs, hypomethylating agents.

Prognosis

There are no large prospective studies analyzing different prognostic factors and their effects on the treatment regimens in patients with MS owing to the rarity of the disease and the variation in location of tumor, timing of presentation, tumor genetics, and treatment strategies. Consequently, at present, there are no validated prognostic factors for MS which can help in risk stratification of patients and treatment planning. Age, gender, or underlying systemic disease does not affect the prognosis of the disease. Only few reports compare the prognosis of isolated MS to that of either MS with concurrent AML or AML presenting without MS,

making the impact of MS on prognosis difficult to assess. Patients with MS and concomitant AML are typically younger, have a higher white cell count, and a greater proportion of monocytic differentiation compared with patients with AML without MS. Although overall prognosis of MS is poor with short survival time [23], 5-year survival rates for patients with MS range between 20% and 30%, which appear similar to AML in general [17,40]. Patients with MS and concurrent or relapsed AML are considered to have poor prognosis compared to patients with isolated MS. Isolated MS, if left untreated, typically progresses to AML over 5 to 12 months after diagnosis. The prognostic significance of cytogenetic alterations in the presence of MS is not fully understood. Although the presence of translocation t(8;21) is associated with a relatively good prognosis when treated with standard induction and intensive consolidation chemotherapy, it remains unclear whether this favorable prognosis remains in the presence of extramedullary disease because there are conflicting reports [64,65]. Furthermore, the implications of NPM1 and FLT3-ITD mutations on prognosis of MS are still not clear and data are too scarce for definite conclusions. There is still lack of knowledge to understand why particular leukemia migrates to the skin and soft tissues and becomes refractory to systemic therapy. Clarification of the relevant risk factors that affect the prognosis of MS will guide clinical stratified treatment and prolong OS.

Conclusion and future perspective

In summary, MS is a rare hematological malignancy and is often associated with poor prognosis. The precise mechanism underlying the pathogenesis of MS is unclear. The identification and diagnosis of MS is often challenging. A high index of suspicion, is required. It should be considered in the differential diagnosis of any atypical soft tissue mass at any site. In all cases, a thorough and orchestrated workup, including whole body imaging, tissue biopsy with IHC using broad panels of antibody markers and genetic profiling, and BM biopsy with similar studies is required for accurate diagnosis of MS and its risk stratification which is important to guide treatment. There is no consensus on specific treatment regimen for MS. The current routine management includes systemic AML-type chemotherapy as the first-line of treatment for both isolated MS and MS with concomitant AML in

association with RT and surgical resection of tumor, if possible. Allo-HSCT should be employed as a part of the consolidation therapy in both adult as well as in pediatric patients. HSCT can significantly improve the prognosis of MS. Relapsed MS remains a clinically challenging situation with few therapeutic options.

Larger prospective studies are needed to understand the mechanism(s) of MS development. In addition, future studies should be directed towards sequencing (whole-genome, whole-exome, and RNA sequencing) based analyses of MS samples to understand the different genetic abnormalities associated with MS that will help in better risk stratification of MS patient. To develop a consensus therapeutic regimen of MS, large multicenter collaboration and development of prospective randomized clinical trials is required.

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