

Case Report

Use of Sorafenib in FLT3-Mutant Myeloid Sarcoma: A Case Report

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Introduction

A 53-years old man with FLT3-ITD-mutant Acute Myeloid Leukemia relapsed ten months after hemopoietic allogeneic stem cell transplant as multiple cutaneous Myeloid Sarcomas. Molecular testing was performed on the core-needle biopsy of the lesion and since positive for the FLT3 mutation, a targeted-therapy with the tyrosine kinase inhibitor sorafenib as single agent was started, obtaining a sustained complete response. After 18 months of therapy patient relapsed on the previously involved sites, because of acquisition of sorafenib-resistant mutation and switched to systemic therapy. Sorafenib proved to be able to distribute in skin and subcutaneous tissues and could be safely used. Molecular testing on Myeloid Sarcoma can be therefore an innovative and effective approach in the management of extra medullary leukemia.

Keywords: FLT3 Mutation; Myeloid Sarcoma; Sorafenib; Target-Therapy

Introduction

FMS-Like Tyrosine Kinase 3 (FLT3) is a receptor tyrosine kinase expressed by hematopoietic stem cells whose activity is essential to normal stem cell function and development. Mutations of this gene are described in about 30% of patients with Acute Myeloid Leukemia (AML) [1,2]. These mutations proved to significantly affect the course, prognosis and outcome of AML, for this reason in recent years a huge effort on the study of potential inhibitors of FLT3 has been performed. FLT3 inhibitors act by blocking the proliferative boost due to the mutation, playing a relevant role in the treatment of FLT3-mutant AML, either as monotherapy or in combination with standard chemotherapy, with promising results [3-5].

Hence FLT3 mutation detection, along with other common genetic alterations, has become a gold standard for diagnosis and management of AML [6]. By contrast it is not usually searched for Myeloid Sarcoma (MS) a rare disease that can present as an isolated or multiple extra medullary leukemic tumor, concurrently with or at relapse of AML [7]. In view of the strict relation of

these conditions, we report the case of a patient with FLT3-mutant AML whose disease relapsed after allogeneic stem cell transplant as a MS, on which FLT3 mutation was tested, and since positive, managed by using the FLT3-inhibitor sorafenib, based on the proved synergistic effect of the Tyrosine Kinase Inhibitor (TKI) after Allogeneic Stem Cell Transplantation (allo-SCT) [8].

Case Report

A 53 years old man diagnosed with FLT3-ITD mutated AML was treated with standard induction and consolidation therapy before receiving, in first complete molecular remission, hematopoietic allogeneic stem cell transplant forms an HLA-identical sibling. Complete hematological, cytogenetic and molecular remission was confirmed at the hundred days' post-transplant evaluation. Ten months after transplant a subcutaneous nodule of augmented consistence appeared in the pectoral region. Patient was completely asymptomatic, with normal lab tests and bone marrow evaluation showed negative MRD. Ultrasound of the nodule showed an ovoid shaped mass with a 2 cm diameter and mixed structure. After 1 month of observation, new subcutaneous lesions with similar US features started to appear in the right cervical region, in the context of left deltoid muscle, right intercostal and left dorsal regions, on both thighs and on right tibial surface (Figure1).



Figure 1: A 53-years old man with FLT3-mutant Acute Myeloid Leukemia relapsed 10 months after allogeneic HSCT as multiple cutaneous Myeloid Sarcomas and was successfully treated with sorafenib monotherapy. A close view of one of the rapidly growing nodules and its ultrasound appearance.

All sites presented an increased uptake at PET scan with a SUVmax of 5.22. A percutaneous biopsy of the pectoral nodule was done. Histological examination described the presence of myeloid blasts consistent with the diagnosis of MS, which was confirmed at the immunophenotype that showed: CD68+, CD45+, MPO+, CD117+, CD30+, MIB 1/Ki67 80%, TdT negative, CD20-, CD3-, CD34-, TRKA-. As FLT3-ITD mutation with an allelic ratio of 10,22 was detected in the analyzed specimen, a targeted therapy with sorafenib was started. Sorafenib was administrated at escalating doses till target 800 mg die (400 mg bid), reached in 45 days. Therapy was well tolerated, showing a rapid effect on subcutaneous nodules, which not only stopped to grow out but fully disappear in two weeks. A PET scan was performed showing a Complete Response which was consolidated by DLI infusion ($6,8 \times 10^7/\text{kg}$ CD3+) at week 17 after sorafenib beginning, with no complications and no GVHD manifestations. Six weeks from first DLI, a second infusion ($1 \times 10^8/\text{Kg}$ CD3+) was performed, again no significant complication occurred.

Because of the appearance of diarrhea and palmar-plantar erythrodysesthesia, side effects related to sorafenib, dose was adjusted to alternated 600-800 mg die at the time of first DLI infusion. Due to persistence of diarrhea, sorafenib was reduced to a 600 mg daily 2 weeks from first adjustment with complete resolution of the symptom. Thirty-three weeks from sorafenib start and 8 weeks from the second DLI infusion a firm lesion appeared in the context of left deltoid muscle at level of the insertion in the humerus, turning out to be a single MS relapse site at PET scan, with bone marrow negativity. Radiotherapy (RT) of the lesion (36 Gy) was started obtaining a rapid and complete response. Molecular biology done on the deltoid lesion specimen demonstrated again a positivity for FLT3 mutation, but this time either in the Internal Tandem Duplication (ITD) region and in the Tyrosine Kinase 2 Domain (TKD) at Asp835His. Eighteen months after the start of sorafenib and 5 months after RT a new rapidly growing lesion appeared in left axilla positive to PET scan. Sorafenib was then

discontinued and patient switched to Azacitidine plus DLI obtaining the fourth complete response.

Discussion

Myeloid Sarcoma (MS) is a rare extra medullary tumor composed of immature myeloid cells expressing CD34, CD117, CD68, MPO and TdT negative, characterized by the occurrence of one or more tumor masses that can involve any site of the body. MS may precede myeloid neoplasms, being concomitant to, represent the relapse, or occur de novo. An increased report of MS presentation after allogeneic stem cell transplantation suggested to possibly represent a reduced graft-versus-leukemia effect at extramedullary sites [9,10]. The outcome of MS is poor independently from the setting of onset and median survival is less than 24 months in most cases [11,12]. A variety of chromosomal abnormalities have been described, among which translocation t (8;21) (q22; q22) is regarded as a recurrent one [9]. Although the study of genetic lesions is critical for AML, it is not routinely performed in MS; thus our approach represented an innovation in this setting where only few studies on genetic information are available. Notably Nucleophosmin (NPM) 1 mutation was identified in a set of MS patients, while FLT3-ITD mutation was detected in a 33% of patients presenting with MS and concurrent AML [13,14].

Activating mutations in the FLT3 gene, involving Internal Tandem Duplications (ITD) in the juxtamembrane domain, and missense point mutations in the Tyrosine Kinase Domain (TKD) involving Aspartic Acid Amino Position 835 (D835), are frequently observed in patients with AML, with ITD mutations being much more frequent than TKDs. They are detected in up to 30% of adult AML cases, with an increased incidence in patients with normal karyotype [3,4]. These mutations lead to overexpression or constitutive activation of the tyrosine kinase sustaining tumor growth and are associated with poor prognosis mainly related to increased relapse risk, there is no study describing the impact of FLT3 mutation in MS [4,15]. Several agents targeting FLT3 have been studied among which the oral multi-kinase inhibitor sorafenib, which is able to inhibit the activities of FLT3, VEGFR-2, VEGFR-3, and members of the platelet-derived growth factor receptor family such as PDGFR-beta and Kit both in vitro and in vivo. It is known to potently inhibit FLT3 enzymatic and cellular activities and to induce significant tumor growth inhibition [16,17].

Food and Drug Administration approved sorafenib for the treatment of hepatocellular, renal cell and differentiated thyroid carcinomas; its use has been successfully tested in many non-hematologic neoplasms, mainly angiosarcoma and soft tissues sarcomas [18,19]. Sorafenib is a reasonably safe drug and can be used with no need of drug reduction in renal and/or hepatic dysfunction, side effects are easily managed by dose titration [18]. In the setting of FLT3-ITD positive AML this agent has been tested

in several trials at induction in combination with cytarabine and anthracycline chemotherapy, as in the SORAML trial, despite an excessive toxicity [20]. On the contrary in the setting of relapsed/refractory disease, it proved to be a valuable option either as a single agent or combined with hypomethylating agents [21,22]. Recent data from SORMAIN trial, showed that the risk of relapse or death is significantly reduced by sorafenib maintenance therapy after allo-SCT, possibly related, as postulated by a previous study, to a synergistic anti-leukemic effect of the Tyrosine Kinase Inhibitor (TKI) and the allo-immune effect of the graft [8,23].

Based on these evidences and to patient history, once FLT3-ITD mutation was detected, we choose to attempt a targeted sorafenib-based treatment to our patient. To our knowledge this is the second time a similar approach has been used in clinical practice [24]. Target therapy provides a valuable alternative to traditional chemotherapy, not only in terms of efficacy but also for a significant impact on the quality of life, considering that lower short term toxicity and no need of hospitalization. Interestingly, in our experience sorafenib proved to be able to distribute into skin and soft tissues and, by reaching the sarcoma, to provide a rapid and complete response although the acquisition in the long run of resistances, that could be seen as the proof of its action on MS. A major mechanism of TKI resistance is caused by selection of specific genetic alterations within the target kinase, even though primary resistances to FLT3-TKI monotherapy were proved in approximately 30% of FLT3-mutated AML.

In clinical studies where FLT3-TKD mutations have appeared in addition to ITD ones during disease progression, it remained unclear whether the double mutants were present before or were acquired after treatment with FLT3 inhibitors. Based on this observation a model of clonal evolution explaining the resistance to FLT3 inhibitors proposed that tumor clones with FLT3-ITD may acquire TKD mutation because of treatment genotoxicity, so double mutant clones carrying both FLT3-ITD and TKD mutations, are selected during treatment leading to disease progression and loss of TKI response [25-27]. In the era of precision medicine our experience suggests to detect molecular lesions sensitive to target therapy in MS as it is routinely done in AML, in view of the unquestionable effectiveness we faced. More studies have to be performed for a better understanding of the action of target agents in MS and whether their combination with other agents, such as hypomethylating agents and DLI, could reduce the risk of resistant mutations onset.

Conclusion

We were able to demonstrate that a complete and durable response could be obtained with sorafenib as single agent in MS after allo-HSCT, hence target therapy can be convincingly used in MS driven by molecular testing, thus representing an innovative

approach to this disease that may provide rationale for a genetic-oriented classification and management of MS in the future.

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The authors declare that they have no conflict of interest.

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