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Case Report Open Access

Isolated Extra Medullary Relapse after Allogeneic Stem Cell Transplant in Flt3 Mutated Acute Myeloid Leukemia (Aml) while on Flt3 Inhibitor Sorafenib

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Introduction

FMS-like tyrosine kinase -3 internal tandem duplication (*FLT3* – ITD) activating mutation occurs in about a quarter of patients with Acute Myeloid Leukemia (AML) and its presence has been associated with a higher likelihood of relapse and poor outcomes [1]. Allogeneic Stem Cell Transplant (SCT) offers the only hope for cure for *FLT3*- ITD mutated AML but the relapse rate remains high even after an allogeneic SCT. Sorafenib, is an oral small molecule that has an inhibitory effect on *FLT3* inhibitor signaling and has shown promise in the treatment of *FLT3* mutated AML when used pre- and post-stem cell transplant [2]. Its use in this disease has been shown to improve response rates but has not been shown to prevent relapse [3].

Case Report

Our patient presented at age of 43 with a high white cell count of 106,000 cells per mm3. Bone marrow aspirate and biopsy revealed 95% cellularity and 92% myeloblasts. Karyotyping demonstrated 46XY, inv 9 (q11; q22) in all twenty metaphases analysed. Myeloblasts were positive for both nucleophosmin NPM1 and *FLT3*-ITD mutations and were also CD25 positive [4]. The patient received induction treatment with high dose cytarabine and daunorubicin [5]. Subsequently, as treatment for primary induction failure [6] high dose cytarabine at a dose of 3 grams/m2 every 12 hours was administered for 6 days (25 days after induction). Sorafenib [7] was started at a dose of 400mg twice daily on day 12 of reinduction and continued for 23 days until day -1 of allogeneic SCT from a matched sibling donor. Bone marrow aspirate and biopsy done 3 days prior to transplant admission showed no molecular and morphological evidence of AML. He received a myeloablative HLA identical matched related transplant 60 days after the initial diagnosis of AML. Conditioning consisted of 1200cGy total body irradiation and cyclophosphamide (120 mg/Kg) [8]. Sorafenib was administered at 200 mg twice daily day +35 after SCT [9]. He developed painful grade 3 follicular skin rash 5 days after starting sorafenib [10]. Sorafenib was dose reduced to 200 mg daily secondary to worsening skin rash after seven days of treatment (day +42) and then to 200 mg every other day after 16 days of daily dosing (day +58). His skin rash symptoms persisted and sorafenib was discontinued after 14 days of every other day dosing (day +72). Unfortunately, the patient relapsed 6 days after stopping sorafenib (day +78). Day +79 he received re-induction with high dose cytarabine and sorafenib 400 mg twice daily, sorafenib was discontinued after 8 days of treatment secondary to GI toxicity and was then restarted 3 weeks later (d+108) at 200 mg twice daily. The, dose was subsequently increased 4 days later to 400 mg twice daily and continued at that dose. He went into morphological remission documented by bone marrow aspirate and biopsy done d+128 after SCT. *FLT3*-ITD mutation was still detectable while donor chimerism was greater than 97% donor in whole blood and bone marrow CD3 and CD34 compartments respectively. Sorafenib was dose reduced to 200 mg twice daily on d+128 secondary to poor tolerance of full dose.

He developed hepatopathy, with grade 3 transaminitis of unclear etiology d+140 after SCT. Bilirubin remained normal. A liver biopsy done d+155 did not show any evidence suggestive of sorafenib induced drug toxicity, leukemia or graft versus host disease. Sorafenib was briefly held for 5 days in lieu of the liver biopsy and then restarted at 200 mg twice daily on d+156. Transaminitis improved after empiric treatment with less than 0.5 mg/Kg dose of systemic steroids. Six months post transplant bone marrow biopsy continued to show >97% donor chimerism, morphological remission and was negative for *FLT3*-ITD and NPM1 mutations by PCR. He developed skin nodules and a morbilliform rash day +194 after transplant. Sorafenib was dose reduced to 200 mg once daily on d+196. Biopsy of the rash was positive for grade 2 GVHD while the nodules were consistent with leukemia cutis and positive for *FLT3*-ITD and NPM1 mutations. Repeat bone marrow aspirate and biopsy done day +211 continued to show morphological and molecular remission. Sorafenib dose was increased to 200 mg twice daily and systemic steroids were discontinued on d+211. He was admitted to the hospital d+214 for salvage cyclophosphamide at 50mg/kg/day for two days as treatment for extramedullary relapse. Sorafenib was discontinued on d+ 218 secondary to bloody diarrhea and neutropenic fever. The skin nodules initially regressed after chemotherapy but worsened upon count recovery. He developed new onset neck pain which progressively

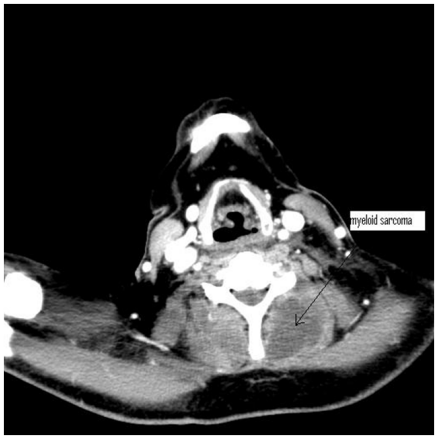

Figure 1: Myeloid Sarcoma.

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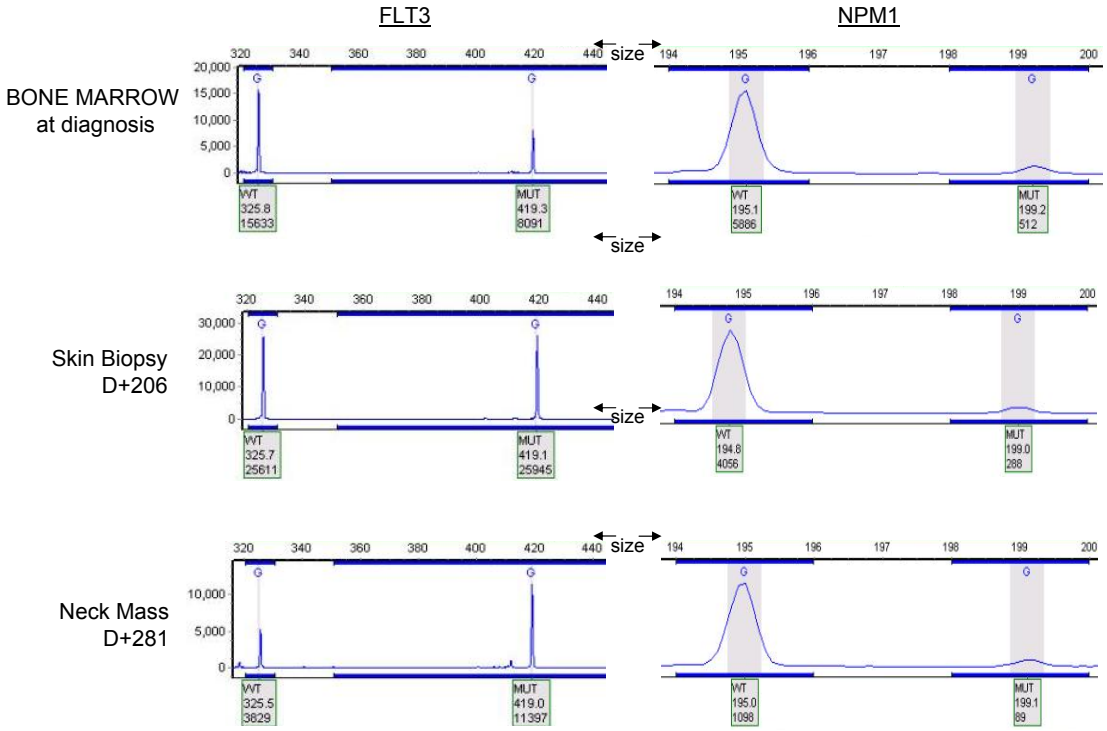

Figure 2: Relative mutant peak level for *FLT3*-ITD versus *NPM1*.

worsened. Transaminitis was noted again and low dose systemic steroids were resumed with modest improvement. Sorafenib was restarted d+248 at 400 mg twice daily and then dose reduced to 200 mg twice daily one week later. He received 3000cGy radiation to the skin nodules with good response but started developing new nodules outside the radiation field. He was subsequently hospitalized d+274 for intractable nausea, diarrhea and worsening neck pain. An MRI of the neck revealed a neck mass. A biopsy of the neck mass was performed and he was diagnosed with myeloid sarcoma (Figure 1) that was positive by Immunohistochemistry for VLA 5 (an adhesion molecule), CD25 and CD43. NPM1 and *FLT3*- ITD mutations were detected. The relative mutant peak level for *FLT3*-ITD versus NPM1 (59 vs 18%) was suggestive of biallelic *FLT3*-ITD mutation (Figure 2). The patient opted for hospice care and passed away a few days later, approximately one year from diagnosis and 289 days after stem cell transplant.

Result and Discussion

This is a unique case of post stem cell transplant extramedullary relapse of *FLT3*-ITD mutated AML in the absence of bone marrow involvement. This relapse occurred while the patient was on the *FLT3* inhibitor sorafenib and in the setting of biopsy proven chronic GVHD of the skin and presumed (not biopsy proven) chronic GVHD of the liver, as suggested by grade 3 transaminitis which responded to systemic steroids.

Conclusion

In our patient, allogeneic stem cell transplant and sorafenib were successful in keeping the marrow free from disease, but unfortunately the leukemia relapsed in extramedullary regions such as the skin and soft tissue. This case report highlights the need to develop novel therapeutic options for patients who relapse after an allogeneic stem cell transplant. In summary *FLT3* inhibitors are useful in the treatment of *FLT3* mutated AML pre and post transplant, but are not sufficient as single agent therapy especially for aggressive forms of leukemia. To date the proper treatment sequence inclusive of chemotherapy, immunomodulatory therapy and stem cell transplantation is not known. Combining novel agents with *FLT3*- inhibitors needs to be explored in patients who relapse after stem cell transplant.

References

1. Schlenk RF, Dohner K, Krauter J, Fröhling S, Corbacioglu A, et al. (2008) Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 358: 909-1918.
2. Metzelder S, Wang Y, Wollmer E, Wanzel M, Teichler S, et al. (2009) Compassionate use of sorafenib in *FLT3*-ITD–positive acute myeloid leukemia: sustained regression before and after allogeneic stem cell transplantation. Blood 113: 6567-6571.
3. Ravand F, Cortes JE, Jones D, Faderl S, Garcia-Manero G, et al. (2010) Phase I/II Study of Combination Therapy With Sorafenib, Idarubicin, and Cytarabine in Younger Patients With Acute Myeloid Leukemia. J.Clin Oncol 28: 1856-1862.
4. Cerny J, Yu H, Ramanathan M, Raffel GD, Walsh WV, et al. (2013) Expression of CD25 independently predicts early treatment failure of acute myeloid leukaemia (AML). Br J Haematol 160: 262-266.
5. AS Stein, O'Donnell MR, Slovak ML, Nademanee A, Dagis A, et al. (2000) High-dose cytosine arabinoside and daunorubicin induction therapy for adult patients with de novo non M3 acute myelogenous leukemia: impact of cytogenetics on achieving a complete remission. Leukemia 14: 1191-1196.
6. Brudler O, Heil G, Kurrle E (1985) High-dose cytosine arabinoside in the treatment of recurrent or acute refractory myeloid leukemias. Onkologie 8: 39-40, 42-43.
7. Levis M, Ravandi F, Wang ES, Baer MR, Perl A, et al. (2011) Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with *FLT3* mutant AML in first relapse. Blood 117: 3294-3301.
8. Blaise D, Maraninchi D, Michallet M, Reiffers J, Jouet JP, et al. (2001) Long-term follow-up of a randomized trial comparing the combination of cyclophosphamide with total body irradiation or busulfan as conditioning regimen for patients receiving HLA-identical marrow grafts for acute myeloblastic leukemia in first complete remission. Blood 97: 3669-3671.

9. Metzelder SK, Schroeder T, Finck A, Scholl S, Fey M, et al. (2012) High activity of sorafenib in *FLT3*-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. Leukemia 26: 2353-2359.

10. Yokoyama H, Lundqvist A, Su S, Childs R (2010) Toxic effects of sorafenib when given early after allogeneic hematopoietic stem cell transplantation. Blood 116: 2858-2859.