Case Report
Next generation sequencing guided treatment modulation and prognosis in Acute myeloid leukemia: Case vignettes

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Abstract: Objective: The genomic mutational landscape of Acute Myeloid Leukemia has contributed to better treatment options, risk stratification and prognostication of this genetically heterogeneous disease. With several approved new drugs targeting specific mutations with better outcomes, we describe here two cases of AML in which, NPM1 was detected at diagnosis. The impact of age, type of treatment, stability of NPM1 mutation, and co-occurring mutations on survival are the essential parameters for investigation. Method: Both the cases of AML were females, >60 years of age with normal 46XX karyotype. Allele specific RT-PCR and fragment analysis was performed for the detection of NPM1-A mutation at diagnosis. Both the patients were unfit for intensive chemotherapy therefore reduced intensity induction chemotherapy regimen was initially administered. Next-generation sequencing was performed for comprehensive mutational profiling, which guided targeted treatment, prognostic stratification, and response assessment. Result: We report that the older AML patients with NPM1 mutation may not have a good outcome with intensive chemotherapy, especially patients with concurrent DNMT3A/IDH-1/2 mutations. In the second case with mutated NPM1, concurrent FLT3-ITD mutation served as a therapeutic target. The FLT3 inhibitor used in combination with standard therapy showed promising results in this case. Conclusion: Here, we emphasize on the utility of next generation sequencing in guiding the treatment initiation or modulation during the disease course and risk stratification in AML. In conclusion, conventional chemotherapy in AML gives very poor overall survival rates and targeted chemotherapy against specific mutations may drastically improve patient survival and treatment outcomes.

Keywords: Acute myeloid leukemia, NPM1, FLT3-ITD, allelic ratio, DNMT3A, IDH1/2, next-generation sequencing

Introduction

Acute myeloid leukaemia (AML) is a rapidly advancing aggressive haematological malignancy characterised by genetic alterations in normal myeloid precursors leading to uncontrolled proliferation, causing impaired haematopoiesis and bone marrow failure [1]. The incidence of AML is 4.3 per 100,000 (age-adjusted) annually with a median age at diagnosis of 68 years and a poor 5-Year period survival of 29.3% in the United States alone [2]. Despite the advancements in AML research, increased risk of relapse/refractory disease is common and high mortality rate is reported as no single superior approach is promising for its treatment [3]. The recent advent of novel therapies has changed the outlook of AML with eight new drugs approved in the last decade for both fit and unfit patients of AML (Table 1). Five of these new drug discoveries are attributable to the better understanding of the molecular architecture of AML.

There has been an incredible surge in our understanding of the mutational landscape of AML [4-6], which has introduced modifications in the existing AML classification and transformed the prognostic stratification, treatment and response assessment of AML [7, 8]. “Passenger lesions” (TET2, DNMT3A, GNAS, ASXL1, SF3B1, PPM1D) have been identified, which
## Role of NGS in AML

### Table 1. Novel therapies approved in AML

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name</th>
<th>Function</th>
<th>Use</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A) Drugs not Targeting any specific Mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>CPX-351</td>
<td>Liposomal formulation of AraC and Daunorubicin</td>
<td>Secondary AML as front-line treatment</td>
<td>March 2017</td>
</tr>
<tr>
<td>2.</td>
<td>Gemtuzumab Ozogamicin</td>
<td>Inhibitor of hedgehog signaling pathway</td>
<td>CD33+ AML alone or in combination with CT for newly diagnosed or R/R AML</td>
<td>September 2017</td>
</tr>
<tr>
<td>3.</td>
<td>Glasdegib</td>
<td>Inhibitor of hedgehog signaling pathway</td>
<td>Combination with LDAC for patients with newly diagnosed AML &gt;75 yrs or with comorbidities</td>
<td>November 2018</td>
</tr>
<tr>
<td></td>
<td>A) Drugs Targeting Molecular Target Points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Midostaurin</td>
<td>Mutated FLT3</td>
<td>Newly diagnosed AML in combination with standard chemotherapy</td>
<td>April 2017</td>
</tr>
<tr>
<td>2.</td>
<td>Gilteritinib</td>
<td>Inhibitor of FLT3 and AXL</td>
<td>Approved for R/R FLT3 mutated AML</td>
<td>November 2018</td>
</tr>
<tr>
<td>3.</td>
<td>Enasidenib</td>
<td>Inhibitor of IDH2</td>
<td>Approved for R/R AML with an IDH2 mutation</td>
<td>August 2017</td>
</tr>
<tr>
<td>4.</td>
<td>Ivosidenib</td>
<td>Inhibitor of IDH1</td>
<td>R/R AML with an IDH1 mutation</td>
<td>July 2018</td>
</tr>
<tr>
<td>5.</td>
<td>Venetoclax</td>
<td>Inhibitor of Bcl-2, independent of TP53 mutations</td>
<td>Newly diagnosed AML unfit for intensive chemotherapy in combination with HMAs/LDAC</td>
<td>November 2018</td>
</tr>
</tbody>
</table>
are initiator mutations present at a low allelic frequency during the beginning of the disease and are insufficient to lead to AML. The incidence of these mutations also known as ‘CHIP’ mutations (clonal hematopoiesis of indeterminate potential) [9-12] progressively increase with age to an incidence of ~10% in normal population older than 70 years with a risk of evolution to myeloid neoplasms at 1% per year. Few disease defining mutations with higher risk, also known as “driver mutations” like BCR-ABL, JAK2, RUNX, FLT3, KRAS, HRAS, called as clonal hematopoiesis of oncogenic potential (CHOP) have also been identified. An average of 13 genes per patient of AML were found to be mutated (23 genes being recurrently mutated). Moreover, half of the patients carried at least one sub-clone along with the founder clone [6]. There is partial adoption of these mutations into the clinical practice by European leukemia network (ELN) and National comprehensive Cancer network (NCCN). Both ELN and NCCN recommend NPM1, FLT3, CEBPA (biallelic), RUNX1, ASXL1 and TP53 testing for all patients with newly diagnosed AML. The NCCN also recommends testing for IDH1/2 and c-KIT (CBF-AML). Based on these mutations, these guidelines risk stratify the patients and personalise treatment [8].

Here, we discuss two cases of AML and report their treatment outcome and disease course wherein either the treatment initiation or modulation was guided by Next Generation Sequencing.

Case 1

A 68-year-old obese woman with type II Diabetes, had history of fever and repeated blood transfusions over the past two months. On evaluation, she was found to have anaemia, thrombocytopenia, and a white blood cell count (WBC) of 51,700 cells/mm\(^3\). Her bone marrow aspirate showed 60% CD45 dim positive myeloblasts which were immunoreactive for CD13, CD33, CD117 and were CD34dim. The blasts did not express cMPO, CD79a, cCD3, CD19, CD14, and HLA-DR. The patient was classified as M1 under the FAB classification (Figure 1). Cytogenetics studies showed normal 46XX karyotype. Molecular studies revealed NPM1-A mutation by allele-specific oligo PCR. Other molecular markers including RUNX1-RUNX1T1, CBFB-MYH11 fusion transcripts and FLT3-ITD and FLT3-TKD mutations were not detected. Considering the age and poor performance status, patient was started on single agent Decitabine therapy (20 mg/m\(^2\)/day IV for 5 days). After four cycles, the bone marrow was documented to be in complete morphological remission. However, the qualitative PCR for NPM1-A mutation remained positive. After eight cycles of decitabine, blasts reappeared in the peripheral
Role of NGS in AML

blood (10%) and the bone marrow (22%). The patient was given a reduced intensity 3 + 5 induction chemotherapy regimen with Daunorubicin (45 mg/m²/day IV on days 1 to 3) and Cytarabine (100 mg/m²/day continuous IV infusion on days 1 to 5), following which morphological, immunophenotypic (<0.1%) and molecular remission (negative NPM1-A on ASO-PCR) was documented. Consolidation therapy with two cycles of high-dose cytarabine (HiDAC, 2 g/m² IV BD on days 1, 3, and 5, Total = 12 g/m²) was given.

A second relapse was seen after seven months with 84% blasts and the immunophenotypic profile similar to diagnostic time point. The patient also had chest infection at this point. The NPM1-A mutation was detected at second relapse at mutant to wild-type allelic ratio of 0.8 by fragment analysis. Targeted NGS revealed DNMT3A (p.R882H; COSM52944), and IDH1 (p.R132H; COSM28746) missense mutations in addition to NPM1-A (p.W288Cfs*12; c.860_863dupTCTG). The NPM1 (VAF: 0.42), DNMT3A (VAF: 0.42), and IDH1 (VAF: 0.38) genes had a median VAF ≤0.5, suggesting these to be heterozygous mutations carried by most cells in the specimen rather than a subpopulation of the sequenced cells.

The patient was started on broad-spectrum antibiotics initially with prophylactic voriconazole and had responded. The fever and chest symptoms decreased. A combination regimen of Azacitidine (75 mg/m²/day SC for 7 days) and Venetoclax (10 mg PO OD on day 1, ramped up to 100 mg PO OD by day 4 due to co-administration with voriconazole) was initiated. Venetoclax was however stopped on day 9. The leucocytosis subsided quickly with complete clearance of peripheral blasts and appearance of severe pancytopenia. The patient again developed a recurrence of febrile neutropenia and succumbed to sepsis subsequently on day 19 of therapy.

Case 2

A 64-year-old lady with obesity and Type II Diabetes mellitus presented with complaints of increasing fatigue and worsening of anaemia over a period of four months. On evaluation, the peripheral blood smear showed 75% myeloblasts which were CD45dim+ with immunoreactivity for CD33, CD13, CD123, CD56+, HLA-DR-, CD7-, CD14-, CD64-. The haemoglobin, TLC and platelet count of the patient over the course of treatment have been summarised in Table 2. Molecular workup revealed a normal 46XX karyotype with mutations in NPM1-A (mutant to wild type allelic ratio

Figure 2. Morphological and flow cytometric characterization of blasts from case 2. (A) Peripheral blood smear showing myeloblasts (Jenner Giemsa; 1000X) (B) myeloblasts with cytochemical reactivity for Myeloperoxidase (1000X); (C-H) Blasts are CD45dim+, CD13+, CD33+, CD123+, CD117dim+, CD56+, HLA-DR-, CD7-, CD14-, CD64-.
Role of NGS in AML

Table 2. Periodic changes in CBC parameters over the duration of treatment

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Hb (g/dL)</th>
<th>TLC (/mm$^3$)</th>
<th>Platelets (/mm$^3$)</th>
<th>Blast (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>6.7</td>
<td>4200</td>
<td>186000</td>
<td></td>
</tr>
<tr>
<td>Time of Presentation</td>
<td>8.2</td>
<td>9200</td>
<td>36000</td>
<td>75</td>
</tr>
<tr>
<td>D9 of 1# AZA</td>
<td>8.2</td>
<td>5520</td>
<td>5200</td>
<td>35</td>
</tr>
<tr>
<td>Post 1# AZA</td>
<td>7.4</td>
<td>4900</td>
<td>4000</td>
<td>1</td>
</tr>
<tr>
<td>Post 2# AZA+Sorafenib</td>
<td>9.2</td>
<td>4400</td>
<td>17000</td>
<td>0</td>
</tr>
<tr>
<td>Post 3# AZA+Sorafenib</td>
<td>7.1</td>
<td>4500</td>
<td>57000</td>
<td>0</td>
</tr>
<tr>
<td>Post 4# AZA+Sorafenib</td>
<td>6.8</td>
<td>5380</td>
<td>79000</td>
<td>0</td>
</tr>
<tr>
<td>Post 5# AZA+Sorafenib</td>
<td>8.9</td>
<td>3570</td>
<td>118000</td>
<td>0</td>
</tr>
<tr>
<td>Post 6# AZA+Sorafenib</td>
<td>9.7</td>
<td>3400</td>
<td>153000</td>
<td>0</td>
</tr>
<tr>
<td>Post 7# AZA+Sorafenib</td>
<td>11.7</td>
<td>6430</td>
<td>187000</td>
<td>0</td>
</tr>
<tr>
<td>Post 8# AZA+Sorafenib</td>
<td>11.6</td>
<td>8170</td>
<td>115000</td>
<td>0</td>
</tr>
<tr>
<td>Post 9# AZA+Sorafenib</td>
<td>11.5</td>
<td>7060</td>
<td>154000</td>
<td>0</td>
</tr>
<tr>
<td>Last Follow up</td>
<td>11.8</td>
<td>5970</td>
<td>179000</td>
<td>0, Flow-CR</td>
</tr>
</tbody>
</table>

= 0.75) and FLT3-ITD (mutant 1 = 32 bp insertion; allelic ratio = 0.12 and mutant 2 = 41 bp insertion; allelic ratio = 0.4). Other common molecular markers including RUNX1-RUNX1T1, CBFB-MYH11 fusion transcripts and FLT3-TKD mutation were not detected. Mutations in NPM1 (p.288Cfs+12; c.863_864insCCTG; COSM28937), and TP53 (p.195T; COSM116924 and p.V274D; COSM44448 and p.F270I; COSM437484) genes were detected by NGS. On account of poor performance status (ECOGII) and relatively advanced age, she was deemed ‘unfit’ for intensive chemotherapy, and was instead started on azacitidine (75 mg/m$^2$/day SC/IV for seven days) and low-dose cytarabine (LD-AraC, 20 mg SC BD) therapy. In view of FLT3-ITD positive status, sorafenib (200 mg PO BD) was added from second chemotherapy cycle onwards. Post four cycles of therapy, patient attained both complete morphological and immunophenotypic remission. A year after the initial diagnosis, having completed 12 cycles with no significant toxicities, she continues to be in remission.

Discussion

The NPM1-mutated AML is the largest genetic group accounting for ~30% of all AML across both young and older patients and up to 50-60% of cytogenetically normal AML where it is slightly more common in females (56.2% vs. 43.8%) [7, 13-15]. The outcome is dependent upon the age of presentation [16-18], karyotype [15], co-occurring mutations especially short lasting. The NGS performed at relapse revealed additional mutations including DNMT3A$^{R882H}$ and IDH1$^{P132}$. Whether these mutations were present at baseline could not be established due to inadequate sample. Moreover, at baseline the NPM1-A mutant to wild-type allelic ratio could not be determined because of unavailability of the assay at that time. The impact of age, type of treatment, stability of NPM1 mutation, co-occurring mutations on the survival are the essential points of discussion in the present case.

The favourable impact of NPM1 mutation is diminished markedly in the older patients treated with intensive chemotherapy especially in the patients of >65 years with worse CR-rate (53% vs. 88%) and 2-year OS in the NPM1+FLT3-ITD cohort (27% vs. 70%; p<0.001) as compared with 55-65 year age group [20]. The outcome of HMA appears inferior in context of CR (28% vs. 56%) and survival (6 vs. 10.8 months; P = 0.076) as compared to intensive chemotherapy in >65 years although it is confounded by the fitness/performance status [18]. However, when HMA is combined with venetoclax, it appears to be more effective than intensive chemotherapy despite older age or poor fitness [18].

The NPM1 mutations are usually secondary events following DNMT3A, IDH1, or NRAS mutations, but remains stable during the disease as in the present case [7, 24]. There are several
mutations which are gained (WT1, FLT3-ITD/TKD, IDH-1/2, TP53, RAS) and lost (FLT3-TKD, RAS, PTPN11, CEBPA) during the relapse. The presence of IDH1 R132H in addition to NPM1/DNMT3A like in the present case [19], portends poor prognosis which is irrespective of the age when treated with intensive chemotherapy and an important finding in contrast to FLT3-ITD co-mutation which has an impact only in the younger subset and not in the older cases [15]. The IDH1/2 co-mutations achieve better CR rates than IDH-wild type patients when treated with HMA+venetoclax combination and remains to be seen how durable they are in long-term follow up [18].

Venetoclax, an inhibitor of Bcl-2 has been approved by FDA to be given in newly diagnosed AML patients who seem to be unfit for intensive chemotherapy in combination with HMA for its remarkable activity and tolerability [25]. The maximum sensitivity was demonstrated in patients with NPM1 mutation and IDH-1/2 mutations. Venetoclax in combination with HMA at a low-intensity regimen has shown promising efficacy and a tolerable safety profile in elderly patients with AML. The HMA+Venetoclax combination appears to be promising in this subset of patients as its associated with low early mortality rates, a high CR + CRi rate of 73%, and OS >17 months [26]. Therefore, a comprehensive NGS panel is crucial in characterising these patients and would also be useful in treatment planning.

The learning from case 1 is that, NPM1 mutated AML is a heterogenous category with diverse prognosis with age and co-occurring molecular mutations. The interactions between the mutations require more understanding in the future studies. At the same time, therapeutic decisions should take into account the molecular information in addition to fitness for intensive chemotherapy. Older AML patients with NPM1 mutation may not have a good outcome [27] as compared to the younger patients with intensive chemotherapy especially patients with concurrent DNMT3A/IDH-1/2 mutations.

In the absence of FLT3-ITD mutations, NPM1 mutations are prognostically favourable [28]. It is well documented that the non-favourable impact of FLT3-ITD surpasses the prognostic benefit of NPM1 mutation [29]. Stratification using both NPM1 and FLT3-ITD markers identified three prognostic groups: NPM1*FLT3-ITD (good), NPM1/FLT3-ITD or NPM1+FLT3-ITD* (intermediate) and NPM1/FLT3-ITD* (poor) [29] assigning an intermediate risk category to our case 2. In cytogenetically normal AML, the frequency of FLT3-ITD ranges from 28-34%, whereas 39% in AML with NPM1 mutation [7]. FLT3 (FMS-like tyrosine kinase) is a transmembrane tyrosine kinase that is assigned to receptor tyrosine kinases (RTK) class III. These receptors are triggered by ligand binding that initiates a pro-proliferative signaling cascade. Approximately 30% of the AML patients have activating mutations in FLT3 and these are not restricted to any specific AML subgroups. FLT3 internal tandem duplication (ITD) mutation within the cytoplasmic juxtamembrane (JM) region occurs at higher frequency (~25%) as compared to point mutations in the activation loop of the tyrosine kinase domain (FLT3-TKD mutation), such as the D835Y mutation (~7%) [13]. The FLT3-ITD mutations are associated with short duration of remission, high relapse rates after conventional induction therapy and poor prognosis [30]. When treated with conventional chemotherapy, patients with FLT3-ITD mutation and normal karyotype have reduced overall survival (OS) [31]. The levels of the cytokine FLT3 ligand rise two- to three-log-fold in response to chemotherapy, and blasts with mutated FLT3-ITD are exquisitely sensitive to the rise in FLT3 ligand levels. This suggests that post chemotherapy, this patient’s residual blasts would be exposed to an environment rich in FLT3 ligand and, hence, conducive to their continued growth; a phenomenon which explains the increased relapse rate and reduced overall survival reported in FLT3-ITD AML patients [32].

The length of in frame duplicated DNA in FLT3-ITD is variable and can range from three to greater than 400 base pairs (bp). Although the exact site of insertion varies from case to case [33], but it is primarily in frame and therefore generates a protein with functional kinase domain. It is reported that the frequency of FLT3-ITDs in an individual patient may vary from one to five different mutants of varying sizes and relative levels [34]. In our case 2, we detected two FLT3-ITD insertions of variable lengths. Discrepancies exist with regard to the FLT3-ITD mutation, although longer ITD length is associated with higher risk of relapse but this assessment is not included in the routine risk
The inserted DNA may be of functional significance [37]. These insertions lead to constitutive activation of the receptor [38] and are associated with leucocytosis, a high percentage of bone marrow blasts, higher relapse incidence, and reduced disease-free survival [35, 39, 40].

One of the key factors that may influence the prognostic impact of FLT3-ITDs is the mutant/wild-type allelic ratio (AR) [33, 37]. Patients with AML harbouring FLT3-ITD with a high (≥0.5) allelic ratio have poor outcomes [41-43]. Recently, the 2017 ELN recommendations categorised FLT3-ITD genotypes based on the ITD allelic ratio and the NPM1 mutational status into four distinct molecular subgroups [44]. However, it is proposed that NPM1 and FLT3-ITD mutations alone are insufficient factors in AML prognosis, and the occurrence of DNMT3A mutation, may influence the decision-making for treatment options in NPM1-mutated AML [7, 45]. More recently, the prognostic impact of NPM1/FLT3-ITD+ mutation in adult AML was shown to be age-dependent [46]. Of note, FLT3-ITD indicated poor survival in younger patients (<60 years) but had no effect in older patients (60-74 years), whereas NPM1 mutation indicated better survival in older patients as compared to younger patients. In patients with NPM1 and FLT3-ITD dual mutations, the survival was less dependent on age than in the other molecular subgroups that is applicable in our case.

The TP53 mutations in de-novo AML are reported at a frequency of 5-10%. Patients with wild-type TP53 had significantly higher incidence of NPM1, FLT3-ITD and DNMT3A mutations as compared to the AML cases with TP53 mutations [47]. The presence of TP53 mutations is significantly associated with chemo-resistance, poor overall and disease-free survival. These mutations primarily occur in the TP53 region encoding DNA-binding domain covering exons 5-8. Of note, six mutational hot-spot codons were identified R175, G245, R248, R249, R273 and R282, of which R273 and R248 are recurrently mutated in AML [48]. The impact of these mutations on TP53 protein is either by direct disruption of the DBD or induction of conformational changes, thus resulting in impaired TP53 function. In our case 2, although the mutations in TP53 were identified in the DBD region (I195T, V274D and F270I) but none of them were hot-spot residues hence implicating their relevance as most likely neutral in nature.

The FLT3 has emerged as a therapeutic target in AML and FLT3 inhibitors have shown promising results in combination with standard therapy. Both FLT3 and NPM1 status have influence on risk stratification and the presence of FLT3-mutation, guides the inclusion of the multikinase inhibitor midostaurin [49] into primary treatment as was given in our patient. Moreover, these inhibitors are included as front-line drug and maintenance therapy after consolidation chemotherapy, in relapsed/refractory disease, or allogeneic stem cell transplantation. Midostaurin is a multi-targeted kinase inhibitor and when combined with standard chemotherapy in patients with FLT3-mutated AML, its known to prolong the overall survival (OS) and event-free survival (EFS) [50]. However, its use is limited by its cost, especially in resource limited countries including India. Sorafenib is a type II FLT3 inhibitor as it acts on both the active and kinetic state of the receptor. Tao et al [20] showed that mono-chemotherapy + Sorafenib significantly improved the overall response rate (ORR) but not the overall survival and relapse-free survival. In patients ≥60 years of age, sorafenib combined with 7 + 3 showed two times better 1-year OS for the FLT3-ITD-mutated patients than the control group.

Conclusion

In the ever-evolving era, where molecular characteristics of almost every disease play a role in disease classification, prognostication and targeted therapy, AML is no exception. ELN and NCCN have recommended genetic testing for all new cases of AML for NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1. Molecular testing is useful in not only predicting outcome but also helps in detecting actionable mutations such as FLT-3, IDH-1, IDH-2, NPM1 and CBF. Small sub-clones harbouring an unfavourable genetic mutation might later relapse as dominant clone and thus may require treatment as unfavourable or high-risk in the beginning of treatment itself. In the new NGS era, the current costs of this technique in a high output, resource limited healthcare system will progressively become more affordable and hence NGS will be accessible ubiquitously. Conventional chemotherapy in
AML gives very poor overall survival rates and targeted chemo-immunotherapy against specific mutations may drastically improve patient survival and outcomes.

Disclosure of conflict of interest

None.

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Role of NGS in AML


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