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CLINICAL VIGNETTE

Treatment of Acute Myeloid Leukemia in the Elderly

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Background

Acute myeloid leukemia (AML) is the second most common type of leukemia in adults, predominantly diagnosed in the elderly with median age of 68, and over 60% of newly diagnosed cases occurring in adults over 60 years of age.[1] Unfortunately, older patients with AML are also more prone to complications from their treatment and worse clinical outcomes overall.[2] Post-induction chemotherapy is a significant component of the treatment regimen for AML based on data showing that almost all patients relapse after achieving their first complete remission, within weeks to months, without further treatment.[3] This portion of therapy is particularly problematic for the elderly as the standard therapy for young patients, high dose cytarabine, is not well tolerated and is not recommended for the elderly. The optimal post induction therapy is unknown in the elderly.[2]

We present a case of an 81-year-old male who went into complete remission from conventional "7+3" induction chemotherapy. He then had post induction maintenance with decitabine for two cycles, which was discontinued early secondary to drug related toxicities. Without further consolidation therapies, he continues to be in remission more than a year since his last treatment.

Case Presentation

An 81-year-old Caucasian man presented to hematology after routine labs showed new onset anemia and blasts. One month prior to presentation, he was hospitalized for fevers, night sweats and productive cough, and had been treated with two courses of antibiotics for pneumonia. His hospital course was also complicated by a new onset atrial flutter, for which he was started on diltiazem and anticoagulation. When presenting in the hematology clinic, he reported that he was recovering from the infection and overall felt well, without fevers, night sweats or weight loss. Laboratory studies showed hemoglobin of 9.8, hematocrit of 29.9, MCV of 100, and blasts in the differential. Flow cytometry confirmed 9% blasts in the blood. Bone marrow biopsy showed 67% marrow involvement with myeloid leukemic cells, positive for the NPM1 and TET2 mutation on sequencing, while negative for the FLT3-ITD mutation. Induction chemotherapy with conventional "7+3" chemotherapy regimen (7 days of standard-dose cytarabine (Ara-C) and 3 days of daunorubicin), was initiated soon thereafter.

After induction chemotherapy, repeat bone marrow biopsy was negative for residual leukemia. He was started on post remission chemotherapy with decitabine intravenously for 5 days every 28 days. However, he was only able to tolerate two cycles with this regimen, as it was complicated by one month of severe pancytopenia, with severe neutropenia (absolute neutrophil count as low as 100), thrombocytopenia to as low as platelets of 18, and a relative anemia with hemoglobin around 10 g/dl.

Once the decitabine was stopped, the cell counts started to recover. Repeat flow cytometry was negative for recurrence of blasts. He continues to be doing well at this time, more than one year after his last therapy with no symptoms or evidence of leukemia recurrence.

Discussion

The prognosis for AML in the elderly is poor, due to treatment-related complications and resistance to therapy.[4] According to the SEER data, younger patients, with the age cut off being less than 60 years of age, have a 30-35% chance of cure, while only 5% of elderly patients with AML are cured.[1] Older persons cannot tolerate aggressive therapies due to poor baseline functional status, other medical comorbidities, decreased ability to clear the chemotherapy, and inability to overcome systemic bacterial and fungal infections for which they are more prone to with the chemotherapy.[5] In addition to more treatment related mortalities, the elderly have disease with more unfavorable AML characteristics, including unfavorable cytogenetic findings (abnormalities of chromosome 5 and 7 or complex chromosomal aberrations), intrinsic drug resistance, presence of dysplastic changes and antecedent hematopoietic disorders, which increases resistance to treatment.[5-7]

In this case report, the patient is considered elderly by age criterion, however, he had good functional capacity previous to chemotherapy, normal hepatic and renal function and was generally healthy, with more favorable AML characteristics on presentation. Therefore, standard induction therapy was chosen. Intensive induction therapy, which is the combination of an anthracycline and cytarabine "7+3" remains the standard of care in patients considered medically fit, and complete remission rates ranges from 65% to 75% in younger adult patients

and from 40% to 60% in older patients.[4] However, remissions are of short duration, and cure is rarely observed. After achieving a first complete remission, post-remission therapy is imperative to avoid relapse.[8]

Post-remission therapy options include standard-dose Ara-C regimens, high-dose Ara-C (HIDAC) regimens, hypmethylating agents, like decitabine used in this patient, or investigational approaches. According to the Cancer and Leukemia Group B trial of post-remission therapy for AML, patients younger than 60 years of age who received HIDAC were more likely to remain in remission and to survive longer than similar patients with lower doses of Ara-C. Forty four percent of the group under 60 treated with HIDAC remained in remission after four years, with only a few reported relapses, whereas only 24% of those with the lower dose Ara-C regimen remained in remission in the same timeframe. The results from the study showed a statistically significant dose-response effect of cytarabine in AML, making HIDAC the standard of care for consolidation therapy in AML in younger people.[9]

However, high dose Ara-C is not recommended for elderly patients, due to increased toxicity from the cytarabine, such as myelosuppression and neurologic side effects. Treatment alternatives for elderly patients include supportive care, low intensity treatment, such as low-dose cytarabine (LDAC) or decitabine, or investigational studies. Studies show that LDAC is well-tolerated in the elderly, with complete remission rates of 15-20%, however, overall survival remains about 5-6 months.[10] When comparing decitabine with mostly LDAC or supportive measures, decitabine has an increase in overall survival to about 7.7 months compared to 5.0 months.[11] This was the treatment chosen in this patient but he still only tolerated two cycles of therapy due to severe cytopenia.

Treatment of older patients with AML remains limited, and enrolling in clinical trials is strongly recommended if eligible. There is a current phase II randomized study which includes the elderly or patients otherwise unfit for cytoxic chemotherapy with AML and investigates activity of prolonged azacitidine combined with two different schedules of the histone deacetylase inhibitor "entinostat".[12] The aim of the study is to determine whether sequential therapy schedule has an improved clinical response as compared to the previously studied concurrent therapy schedule for entinostat. More studies focused on the elderly are needed to fine tune treatment strategy for this patient population.

REFERENCES

1. **National Cancer Institute.** SEER Stat Fact Sheets. seer.cancer.gov/statfacts/html/amyl.html. Accessed January 2018.
2. **Rowe JM.** Optimal induction and post-remission therapy for AML in first remission. *Hematology Am Soc Hematol Educ Program.* 2009:396-405. doi:10.1182/asheducation-2009.1.396. Review. PubMed PMID: 20008225.
3. **Cassileth PA, Harrington DP, Hines JD, Oken MM, Mazza JJ, McGlave P, Bennett JM, O'Connell MJ.** Maintenance chemotherapy prolongs remission duration in adult acute nonlymphocytic leukemia. *J Clin Oncol.* 1988 Apr;6(4):583-7. PubMed PMID:3282032.
4. **Pulsoni A, Pagano L, Latagliata R, Casini M, Cerri R, Crugnola M, De Paoli L, Di Bona E, Invernizzi R, Marmont F, Petti MC, Rigolin G, Ronco F, Spadano A, Tosti ME, Visani G, Mele A, Mandelli F.** Survival of elderly patients with acute myeloid leukemia. *Haematologica.* 2004 Mar;89(3):296-302. PubMed PMID: 15020267.
5. **Klepin HD, Balducci L.** Acute myelogenous leukemia in older adults. *Oncologist.* 2009 Mar;14(3):222-32. doi: 10.1634/theoncologist.2008-0224. Epub 2009 Mar 12. Review. PubMed PMID: 19282349.
6. **Leith CP, Kopecky KJ, Godwin J, McConnell T, Slovak ML, Chen IM, Head DR, Appelbaum FR, Willman CL.** Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood.* 1997 May 1;89(9):3323-9. PubMed PMID: 9129038.
7. **Fialkow PJ, Singer JW, Raskind WH, Adamson JW, Jacobson RJ, Bernstein ID, Dow LW, Najfeld V, Veith R.** Clonal development, stem-cell differentiation, and clinical remissions in acute nonlymphocytic leukemia. *N Engl J Med.* 1987 Aug 20;317(8):468-73. PubMed PMID: 3614291.
8. **Hiddemann W, Kern W, Schoch C, Fonatsch C, Heinecke A, Wörmann B, Büchner T.** Management of acute myeloid leukemia in elderly patients. *J Clin Oncol.* 1999 Nov;17(11):3569-76. Review. PubMed PMID: 10550156.
9. **Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, Omura GA, Moore JO, McIntyre OR, Frei E 3rd.** Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med.* 1994 Oct 6;331(14):896-903. PubMed PMID: 8078551.
10. **Burnett AK, Milligan D, Prentice AG, Goldstone AH, McMullin MF, Hills RK, Wheatley K.** A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer.* 2007 Mar 15;109(6): 1114-24. PubMed PMID: 17315155.
11. **Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, Gau JP, Chou WC, Buckstein R, Cermak J, Kuo CY, Oriol A, Ravandi F, Faderl S, Delaunay J, Lysák D, Minden M, Arthur C.** Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol.* 2012 Jul 20;30(21):2670-7. doi: 10.1200/JCO.2011.38.9429. Epub 2012 Jun 11. PubMed PMID:22689805; PubMed Central PMCID: PMC 4874148.
12. A Trial to Evaluate Two Schedules of MS275 in Combination With 5AC in Elderly Patients With Acute Myeloid Leukemia (AML). (2017). Retrieved from http://clinicaltrials.gov/ct2 (Identification No. NCT01305499).

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