Blood consult: monosomal karyotype acute myeloid leukemia

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Case presentation

A 24-year-old woman presented to her primary care physician for persistent bilateral otitis media and frequent night sweats. Laboratory evaluation revealed a white blood cell count of 26,000/mL with 84% blasts on differential, hemoglobin 6.8 g/dL, and platelet 90,000/mL. Her total serum lactate dehydrogenase level was 888 U/L. She underwent a diagnostic bone marrow aspirate and biopsy, which demonstrated hypercellularity with flow cytometry demonstrating 87% blasts expressing CD4, CD11c, HLA-DR, CD33, CD15, CD64, dim CD117, and partial CD56, but lacking MPO and CD34. Cytogenetic analysis revealed the following karyotype: 45,XY,del(5)(q11.2q35),+8,der,(12)der(16;18)(p10;q10),−7,−17[17]/46,XY[3]. Molecular studies were negative for a FLT3-ITD or mutations in NPM1, CEBPA, or FLT3-TKD. These findings were consistent with a diagnosis of acute myeloid leukemia (AML) with monosomal karyotype (MK+ AML). She was transferred to our medical center for further management.

Review of her medical history demonstrated good health, no prior medications, and no known drug allergies. She has no history of smoking or alcohol. Family history was significant for her maternal grandmother having pancreatic cancer. On physical examination, she was noted to have multiple cervical lymph nodes all less than 0.5 cm with the remaining otherwise completely normal. Her bone marrow specimens were reviewed, and a management decision was made.

Following institutional guidelines, she was given induction chemotherapy consisting of idarubicin 12 mg/m² by intravenous injection on days 1 through 3, and cytarabine 3000 mg/m² by intravenous infusion over 3 hours every 12 hours for 4 days. Her persistent otitis media had been caused by adenoid hypertrophy with subsequent eustachian tube obstruction, which improved after starting chemotherapy. Her course was complicated by neutropenic fever, and workup revealed fungal pulmonary nodules, which were treated with antifungal therapy, and anthracycline-induced pericarditis, which responded to a 14-day course of prednisone.

Fourteen days after the beginning of induction chemotherapy, bone marrow aspirate and biopsy were performed, which revealed hypocellularity and 0% residual blasts. Subsequent bone marrow aspirate and biopsy after peripheral blood count recovery demonstrated hypercellularity with less than 1% blasts and no morphologic or immunophenotypic evidence of disease, and cytogenetics showed normal female karyotype, 46,XX, consistent with a first complete cytogenetic remission.1 HLA typing showed that she and her brother are a 10-of-10 match. She now presents for discussion of treatment strategy after induction therapy.

Discussion

Cytogenetic analysis at time of diagnosis is the foremost predictor of response to induction chemotherapy and survival in AML. MK+ AML is a relatively new cytogenetic category defined by the presence of a clone containing at least 2 autosomal monosomies or a single autosomal monosomy (excluding isolated loss of X or Y) in combination with at least one structural abnormality.2 The overall incidence of MK+ AML is 10% to 15%, it increases with age and occurs infrequently (<5%) in patients younger than 30 years.3-4 MK+ AML is frequently associated with other adverse-risk cytogenetic abnormalities, such as inv(3), −5 or del(5q), −7 or del(7q), abl(17p) and complex karyotype, and is rarely seen in AML with FLT3-ITD or mutations in NPM1 or FLT3-TKD. Alterations in TP53 have been described in approximately 80% of MK+ AML patients.5

MK+ AML responds poorly to conventional chemotherapy and is associated with a worse prognosis than unfavorable karyotype AML. Several recent studies have demonstrated that, among patients with unfavorable karyotype AML, those with MK+ AML have lower rates of complete remission than MK− patients (18%-37% in MK+ vs 34%-58% in MK−).2,4,5 The negative effect of MK+ appears to the less pronounced in younger patients.3 The lower complete remission rate noted in MK+ patients translates into significantly worse survival for these patients (4-year overall survival rates between 3% and 9%).3 The presence of residual normal metaphases, as seen in our patient, appears to have a modest favorable prognostic impact.7

Is there a preferred induction regimen for patients with MK+ AML?

Recently, daunorubicin dose escalation was shown to result in a higher response rate and improved survival in patients with AML younger than 65 years of age.8 Unfortunately, in older patients with MK+ AML, doubling the anthracycline dose did not improve outcomes.9 These results may reflect the significantly higher multidrug resistance activity noted in MK+ AML blasts compared with MK− blasts (P = .026).10 In other studies, induction regimens using high-dose cytarabine compared with conventional dose cytarabine did not appear to be of therapeutic benefit.11 However, the use of high-dose cytarabine-based regimens may improve the outcome of patients with MK+ AML, as 2 recent studies have shown a potential survival benefit with high-dose cytarabine in this subgroup of patients with highly unfavorable karyotype.11,12
What is the optimal postremission therapy for patients with MK+ AML?

As mentioned previously, the outcome of patients with MK+ AML is dismal. Not clear from these original reports is the impact of different postremission strategies on the outcome of these patients. Fang et al\textsuperscript{13} retrospectively reviewed the experience with alloge-neic hematopoietic cell transplantation (alloHCT) in 432 patients with AML treated at the Fred Hutchinson Cancer Research Center in Seattle. They found a 25% 4-year disease-free survival rate in patients with MK+ AML. Similar results were seen with matched related and matched unrelated donors. Although these results were inferior to the 56% survival seen in patients with MK- AML (\(P < .0001\)), they appear to be substantially better than the 3% to 9% survival seen with chemotherapy. Very recently, Kayser et al have confirmed the overall dismal prognosis seen in MK+ AML (9% 4-year overall survival).\textsuperscript{6} Among the minority of younger patients (age, 18-60 years) who achieved a first complete remission, the 4-year survival was 50% for those transplanted in first remission from a matched sibling, 15% for those receiving an unrelated transplant, and 32% for those not transplanted. The outcome for those transplanted in relapse was dismal.

Given the overall poor outcomes of MK+ AML and lack of optimal treatment options, we recommended that our patient proceed to a myeloablative HLA-sibling alloHCT. Currently, data available suggest that alloHCT is a reasonable treatment strategy for patients with MK+ AML with a matched sibling, although the true efficacy of alloHCT for MK+ AML has not yet been demonstrated by a prospective randomized comparative study. For MK+ AML patients in first complete remission lacking a matched related sibling, the optimal postremission treatment strategy has not been defined yet. With improving outcomes of matched unrelated and cord blood transplants, many would recommend transplantation using an alternative donor. An alternative approach might be to treat with chemotherapy and reserve transplant until first relapse, although the outcome of MK+ AML after relapse remains dismal. If transplantation is not offered in first remission, then available data would suggest that postremission therapy include repetitive cycles of moderate- to high-dose cytarabine.\textsuperscript{11,12} These patients are ideal candidates for participation in clinical trials testing novel treatment strategies to improve the overall outcome in this very poor prognostic group.

\section*{References}


\section*{Authorship}

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