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Inotuzumab Ozogamicin, a Nonchemotherapy Option for Relapsed Acute Lymphoblastic Leukemia

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H&O What percentage of patients with ALL will develop relapsed disease, and what is their prognosis?

HK Among adult and elderly patients with acute lymphoblastic leukemia (ALL), approximately 50% to 60% will develop relapsed disease. Survival is higher in the adult patients, at close to 60%. Elderly patients (≥60 years) typically cannot tolerate the intensity of therapy, and approximately 30% will die during the induction phase or while in complete remission. With standard chemotherapy, the cure rate among elderly patients with ALL is only 20%. Historical data for intensive chemotherapy show that once patients relapse, the outcome is very poor. The complete response rates are only 40% in first relapse, 20% in second, and 10% in third. The estimated 3-year survival is less than 10%. Therefore, relapse in adult and elderly patients with ALL used to be similar to a death sentence, with a very poor prognosis.

H&O What are the treatment options beside intensive chemotherapy?

HK There are now targeted therapies. In 2014, the US Food and Drug Administration (FDA) approved blinatumomab (Blincyto, Amgen), a CD3/CD19 antibody construct, for the treatment of relapsed/refractory ALL. In 2017, inotuzumab ozogamicin (Besponsa, Pfizer), a CD22 monoclonal antibody bound to calicheamicin, was approved for the same indication. Also in 2017, the FDA approved a chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel (Kymriah, Novartis), for young patients (≤25 years) with ALL that is refractory or in second or later relapse. (These patients represent a small proportion overall.)

H&O What data led to the FDA approval of inotuzumab ozogamicin in ALL?

HK The pilot studies of inotuzumab ozogamicin at MD Anderson evaluated an intravenous dose of 1.8 mg/m^2 as a single dose or as fractionated doses of 0.8 mg/m^2, 0.5 mg/m^2, and 0.5 mg/m^2 administered intravenously on days 1, 8, and 15. These studies showed a high complete response rate of 50% to 60%. The data led to a randomized study comparing inotuzumab ozogamicin with the best standard of care, which is intensive chemotherapy. The complete response rate was 80% with inotuzumab ozogamicin vs approximately 30% with intensive chemotherapy (Table). Inotuzumab ozogamicin increased

> We encourage the use of inotuzumab ozogamicin, in combination with chemotherapy, in the relapsed/refractory setting.

Table. Rates of Complete Remission in a Phase 3 Trial of Inotuzumab Ozogamicin Versus Standard Therapy in Patients With Acute Lymphoblastic Leukemia[a]

Endpoint	Inotuzumab Ozogamicin Group		Standard-Therapy Group		Between-Group Difference (97.5% CI), percentage points	*P* Value[b]
	n/N	% (95% CI)	n/N	% (95% CI)		
Complete remission or complete remission with incomplete hematologic recovery						
Total	88/109	80.7 (72.1-87.7)	32/109	29.4 (21.0-38.8)	51.4 (38.4-64.3)	<.001
Bone marrow blast results below threshold for minimal residual disease	69/88	78.4 (68.4-86.5)	9/32	28.1 (13.7-46.7)	50.3 (29.9-70.6)	<.001
Complete remission						
Total	39/109	35.8 (26.8-45.5)	19/109	17.4 (10.8-25.9)	18.3 (5.2-31.5)	.002
Bone marrow blast results below threshold for minimal residual disease	35/39	89.7 (75.8-97.1)	6/19	31.6 (12.6-56.6)	58.2 (31.9-84.4)	<.001
Complete remission with incomplete hematologic recovery						
Total	49/109	45.0 (35.4-54.8)	13/109	11.9 (6.5-19.5)	33.0 (20.3-45.8)	<.001
Bone marrow blast results below threshold for minimal residual disease	34/49	69.4 (54.6-81.7)	3/13	23.1 (5.0-53.8)	46.3 (16.2-76.4)	.004

[a]The remission-analysis population includes the first 218 patients who underwent randomization in the intention-to-treat population. Confidence intervals for rates were calculated by means of the Clopper–Pearson method, and confidence intervals for between-group differences were calculated by means of the asymptotic method.

[b]The 2-sided *P* values for between-group differences were determined by means of the chi-square test or Fisher's exact text (if any cell count was <5).

the median survival and improved 2-year survival. However, the median survival remains only approximately 9 months, and the 2-year estimated survival rate is 25%. Inotuzumab ozogamicin represents a major improvement in the treatment of ALL, but we can do better.

H&O How can outcomes be improved?

HK Although blinatumomab and inotuzumab ozogamicin are superior to intensive chemotherapy when administered per the FDA-approved indications, they do not provide a good treatment value because they are very expensive. I foresee new treatment regimens that will consist of the antibodies combined with chemotherapy. My colleagues and I have published studies combining these agents with a chemotherapy regimen known as mini-hyper-CVD, a reduced intensity version of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine). Mini-hyper-CVD consists of cyclophosphamide and dexamethasone at a 50% dose reduction, methotrexate at a 75% dose reduction, and cytarabine at 0.5 g/m^2 for 4 doses. (This regimen omits the anthracycline.) Mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, is associated with a complete response rate of 90% as the first salvage treatment in ALL, with an estimated 3-year survival of 50%. In the second and third salvage settings, the complete response rates are 55% to 60%, with an estimated 2- to 3-year survival of approximately 25%. Study results have been published in peer-reviewed journals, and I recommend that this strategy be adopted in community practice.

The same regimen has been evaluated in elderly patients with frontline ALL. The complete response rate is almost universal, at 95% or higher. The estimated 5-year survival is close to 50%. These outcomes are a major improvement compared with the historical data.

H&O What is the dose of inotuzumab ozogamicin used in clinical practice?

HK Inotuzumab ozogamicin is approved by the FDA for 1.8 mg/m^2 per course. When patients receive an average of 3 to 4 courses, the cumulative dose reaches 5.4 mg/m^2. When these patients undergo allogeneic transplant, the rate of veno-occlusive disease can reach 10% to 20%. Therefore, we have reduced the dose of inotuzumab ozogamicin to 0.9 mg/m^2 during induction with chemotherapy and to 0.6 mg/m^2 for the 3 consolidation doses, for a total dosage of 2.7 mg/m^2. By halving the dose of inotuzumab ozogamicin, combining it with chemotherapy, and providing prophylaxis with ursodiol, the rate of veno-occlusive disease has been reduced to approximately 5% to 7%.

H&O Are there any other notable adverse events?

HK In addition to veno-occlusive disease, myelosuppression can occur.

H&O How can inotuzumab ozogamicin be incorporated into the management plan for patients with ALL?

HK The FDA approval is for patients with relapsed/refractory ALL. We encourage the use of inotuzumab ozogamicin, in combination with chemotherapy, in the relapsed/refractory setting. This regimen can also be used in the frontline setting for elderly patients. We are hoping to combine inotuzumab ozogamicin and blinatumomab with intensive chemotherapy among younger patients (<60 years) with ALL.

The treatment is equally effective among nearly all types of patients. There are a few subsets of patients who respond less well. They include patients with the *MLL* gene rearrangement, those with translocation (4;11), and those who have complex karyotypes with 5 or more chromosomal abnormalities.

H&O Can inotuzumab ozogamicin be combined with other targeted treatments?

HK In addition to chemotherapy, inotuzumab ozogamicin has been combined in an antibody cocktail with blinatumomab. The studies of chemotherapy plus inotuzumab ozogamicin plus blinatumomab are ongoing.

Disclosure

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Suggested Readings

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