blood advances

Implementation of a graduated-intensity approach for acute lymphoblastic leukemia in a Rwandan district hospital

Alexis Manirakiza,[1] Grace Dugan,[1,2] Christina Hanna,[3] Cam Nguyen,[1] Temidayo Fadelu,[4] Esperance Iradukunda,[1] Alexandra E. Fehr,[5] Deogratias Ruhangaza,[6] Elizabeth Albert,[7] Tharcisse Mpunga,[6] Cyprien Shyirambere,[1] and Leslie Lehmann[4,8]

[1]Partners in Health, Rwanda; [2]University of Global Health Equity, Rwanda; [3]Children's Hospital of Philadelphia, Philadelphia, PA; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Athena Institute at Vrije Universiteit, Netherlands; [6]Ministry of Health, Rwanda; [7]University of Pennsylvania, Philadelphia, PA; and [8]Boston Children's Hospital, Boston, MA

Background

Acute lymphoblastic leukemia (ALL) outcomes in low-income countries (LICs) are poor, with only 20% to 50% of patients being successfully treated.[1] Many of the treatment failures are the result of recurrent disease but treatment-related mortality (TRM) is also increased. Hunger et al[2] have proposed graduated-intensity regimens for ALL in resource-limited settings so that capacity for managing toxicity can be built over time without excessive TRM.

The Butaro Cancer Center of Excellence (BCCOE) is based in a rural Rwandan district hospital and uses a task-shifted model of care. General practitioners, pediatricians, and internists provide care using nationally approved treatment protocols and receive remote technical support from cancer centers in the United States. Starting in 2012, BCCOE implemented the low-intensity Hunger 1 regimen to treat ALL patients. Once acceptable TRM was documented, we transitioned to a more intensive regimen, Hunger 2, which incorporates a delayed intensification phase (Table 1).

Table 1. Comparison of Hunger 1 and Hunger 2 regimens[2]

Hunger 1	Hunger 2
Induction (4 weeks)	**Induction (4 weeks)**
Prednisone, IT methotrexate, vincristine, L-asparaginase	Prednisone, IT methotrexate, vincristine, L-asparaginase
Bone marrow biopsy at day 29 determines whether patient is in remission	Bone marrow biopsy at day 29 determines whether patient is in remission
Consolidation (4 weeks)	**Consolidation (4 weeks)**
IT methotrexate, 6-mercaptopurine, vincristine	IT methotrexate, 6-mercaptopurine, vincristine
Maintenance (continued for a total treatment duration of 2.5 years)	**Interim maintenance (8 weeks)**
IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone	IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone
	Delayed intensification (8 weeks)
	IT methotrexate, vincristine, L-asparaginase, dexamethasone, doxorubicin, cyclophosphamide, cytarabine
	Maintenance (continued for a total treatment duration of 2.5 years)
	IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone

IT, intrathecal.

Aims

We aimed to assess the efficacy and safety of a graduated-intensity approach for patients receiving treatment for ALL at BCCOE in Rwanda beginning in October 2016.

Methods

Inclusion criteria

Adult and pediatric patients with a pathology-confirmed diagnosis of ALL who were treated according to the Hunger framework from October 2012 to September 2017 and were included in our study.

Exclusion criteria

Any patient with ALL who received previous treatment with chemotherapy was excluded from the study cohort.

Study design

In this retrospective cohort, primary outcome variables were toxicity and efficacy of the Hunger 1 regimen and early outcomes for patients receiving the Hunger 2 regimen at the end of delayed intensification (24 weeks).

Results

Table 2. Treatment-related mortality and overall survival outcomes of ALL patients treated with Hunger 1 and Hunger 2 regimens at BCCOE

	Hunger 1 end of therapy survival[3]	Hunger 2 end of delayed intensification survival*
No. of patients starting induction phase	40	17
TRM (%)	3	0
Death as a result of disease (%)	75	24
Event-free survival (%)	22	—†

*Data for Hunger 2 from Dugan G. Implementation of the Hunger 2 Regimen for Acute Lymphoblastic Leukemia in the Butaro Cancer Center of Excellence: Toxicity and Interim Outcomes (unpublished master's thesis). Kigali, Rwanda: University of Global Health Equity; 2018.

†Sixty-five percent of patients in clinical remission at the end of delayed intensification.

Conclusions

Graduated-intensity therapy has been proposed for use in LICs to ensure that capacity for managing toxicity is proportional to therapeutic intensity. BCCOE is the first cancer care center to use the Hunger framework for treating patients with ALL in sub-Saharan Africa. This approach mandates thorough monitoring and documentation of toxicity before advancing to a more aggressive regimen.

TRM from Hunger 1 was acceptable, but patients experienced high rates of death as a result of disease (Table 2). BCCOE moved to the Hunger 2 regimen, which involves a delayed intensification phase. Early results indicated continued acceptable toxicity, but we realize that it is too early to comment on efficacy. Once TRM has been captured from this Hunger 2 cohort, Hunger 3 and Hunger 4 will be implemented for high-risk patients.

We are the first to show the feasibility of a novel approach based on graduated intensity in a rural Rwandan hospital. This allowed us to robustly assess our capacity to manage toxicity in a common oncologic diagnosis and to use a method of rapid cycle improvement to implement interventions that allow for increasing treatment intensity.

Acknowledgments

The authors thank the University of Global Health Equity and the Dana-Farber Cancer Institute and Boston Children's Cancer and Blood Disorders Center for ongoing support and technical assistance throughout this research project.

Authorship

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Alexis Manirakiza, Partners in Health, Rwanda; e-mail: alexismanirakiza@rocketmail.com; and Christina Hanna, Children's Hospital of Philadelphia, Philadelphia, PA; e-mail: hannacm@email.chop.edu.

References

1. Bonaventure A, Harewood R, Stiller CA, et al; CONCORD Working Group. Worldwide comparison of survival from childhood leukaemia for 1995-2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries. *Lancet Haematol*. 2017;4(5):e202-e217.
2. Hunger SP, Sung L, Howard SC. Treatment strategies and regimens of graduated intensity for childhood acute lymphoblastic leukemia in low-income countries: A proposal. *Pediatr Blood Cancer*. 2009;52(5):559-565.
3. Rubagumya F, Xu MJ, May L, et al. Outcomes of low-intensity treatment of acute lymphoblastic leukemia at Butaro Cancer Center of Excellence in Rwanda. *J Glob Oncol*.2018;(4):1-11.

DOI 10.1182/bloodadvances.2018GS112622