

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

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## Background

Acute lymphoblastic leukemia (ALL) outcomes in low-income countries (LICs) are poor, with only 20% to 50% of patients being successfully treated.<sup>1</sup> Many of the treatment failures are the result of recurrent disease but treatment-related mortality (TRM) is also increased. Hunger et al<sup>2</sup> 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<sup>2</sup>**

Hunger 1	Hunger 2
<b>Induction (4 weeks)</b> Prednisone, IT methotrexate, vincristine, L-asparaginase Bone marrow biopsy at day 29 determines whether patient is in remission	<b>Induction (4 weeks)</b> Prednisone, IT methotrexate, vincristine, L-asparaginase Bone marrow biopsy at day 29 determines whether patient is in remission
<b>Consolidation (4 weeks)</b> IT methotrexate, 6-mercaptopurine, vincristine	<b>Consolidation (4 weeks)</b> IT methotrexate, 6-mercaptopurine, vincristine
<b>Maintenance (continued for a total treatment duration of 2.5 years)</b> IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone	<b>Interim maintenance (8 weeks)</b> IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone  <b>Delayed intensification (8 weeks)</b> IT methotrexate, vincristine, L-asparaginase, dexamethasone, doxorubicin, cyclophosphamide, cytarabine  <b>Maintenance (continued for a total treatment duration of 2.5 years)</b> 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 <sup>3</sup>	Hunger 2 end of delayed intensification survival <sup>*</sup>
No. of patients starting induction phase	40	17
TRM (%)	3	0
Death as a result of disease (%)	75	24
Event-free survival (%)	22	—†

<sup>\*</sup>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.

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

## References

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## 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.

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## Authorship

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

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