



AIDS-Related Non-Hodgkin's Lymphoma in Sub-Saharan Africa: Current Status and Realities of Therapeutic Approach

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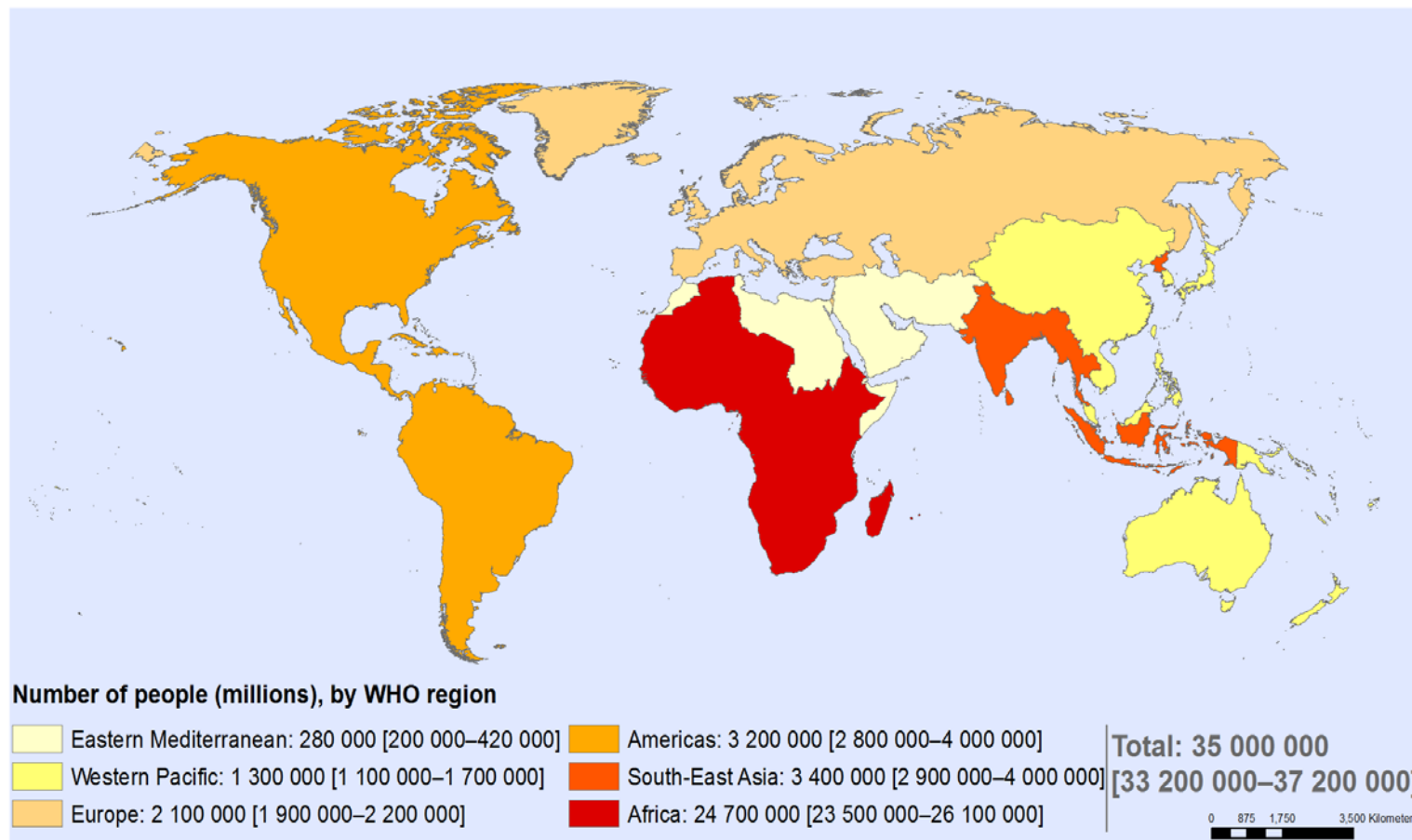
Abstract

Today AIDS-related non-Hodgkin's lymphoma (AR-NHL) is a significant cause of morbidity and mortality in HIV-infected patients the world over, and especially in sub-Saharan Africa. While the overall incidence of AR-NHL since the emergence of combination antiretroviral therapy (cART) era has declined, the occurrence of this disease appears to have stabilized. In regions of the world where access to cART is challenging, the impact on disease incidence is less clear. In the resource-rich environment it is clinically well recognized that it is no longer appropriate to consider AR-NHL as a single disease entity and rather treatment of AIDS lymphoma needs to be tailored to lymphoma subtype. While intensive therapeutic strategies in the resource-rich world are clearly improving outcome, in AIDS epicenters of the world and especially in sub-Saharan Africa there is a paucity of data on treatment and outcomes. In fact, only one prospective study of dose-modified oral chemotherapy and limited retrospective studies with sufficient details provide a window into the natural history and clinical management of this disease. The scarcities and challenges of treatment in this setting provide a backdrop to review the current status and realities of the therapeutic approach to AR-NHL in sub-Saharan Africa. More pragmatic and risk-adapted therapeutic approaches are needed.

Introduction

- Cancer is now a leading cause of morbidity and mortality among individuals living with HIV and AIDS.
- Overwhelming majority of HIV-infected individuals in resource challenged regions are either unaware of their infection or go untreated.
- NHL is the second most common AIDS-related malignancy and most common cause of cancer mortality in AIDS patients.
 - KS is the most common.
- Obstacles that pose problems for clinicians who are managing these patients:
 - Unreliable availability of cART
 - Drugs for treatment of opportunistic infection
 - Poor access to traditional cytotoxic chemotherapy drugs
 - Poor access to supportive therapy.

Adults and children estimated to be living with HIV, 2013 By WHO region



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Data Source: World Health Organization
Map Production: Health Statistics and
Information Systems (HSI)
World Health Organization



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Background

- 22.5 million adults and children are living with HIV infection/AIDS in Sub-Saharan Africa.
- 1.3 million deaths annually attributable to HIV disease.
- 1/3 of HIV-infected individuals residing in Sub-Saharan Africa are eligible for ART and receive appropriate cART and patient care.
- AR-NHL is much more aggressive.
 - Characterized by higher grade (40-60%)
 - Extranodal disease (80%)
 - Advanced clinical stage (60-70%)
 - Present with B symptoms
 - Shortened survival (median 7-8 months).

Diagnosis and Staging

- **Diagnosis of AR-NHL is established by pathological confirmation of malignant lymphoma on biopsy material of involved lymph node(s), bone marrow or extranodal site(s) and should include immunohistochemistry for confirmation of CD20+ status of the tumor.**
- **Routine HIV antibody testing is performed in patients with newly diagnosed NHL.**
- **Patients with AR-NHL are best staged according to the Ann Arbor staging criteria.**

Diagnosis and Staging (2)

- **Physical exam and history include:**
 - **CBC & Differential**
 - **Serum electrolytes & chemistries**
 - **Lactate dehydrogenase (metabolic parameter that is indicative of tumor lysis syndrome)**
 - **Bone marrow aspirate and biopsy**
 - **Examination of the CSF**
 - **Radiographic studies**
 - **Sonography and Echocardiography (if available)**

TABLE 1

Summary of clinical data on the treatment of AIDS-related non-Hodgkin's lymphoma (AR-NHL) in (A) sub-Saharan Africa presented in a hierarchical/strength of evidence approach and (B) the United States presented year of report (most recent) of prospective clinical trials only. [Abbreviations used: Study/Year—trial number; Regimen—study sponsor or group and year reported with AMC: AIDS Malignancy Consortium, CWRU: Case Western Reserve University, ECOG: Eastern Cooperative Oncology Group, NCI: National Cancer Institute, and ACTG: AIDS Clinical Trials Group; LD/SD: low dose/standard dose; Nos. Pts.: number patients; BL: Burkitt's lymphoma; ORR: objective response rate (CR/PR): complete response/partial response; MST: median survival time, 1-yr : 1-year survival rate and OS: overall survival; and cART: combination antiretroviral therapy.].

Regimen (Study/Year) [Reference]	Nos. Pts.	ORR (CR/PR)	Survival	Comment(s)
(A) Sub-Saharan Africa Data—Prospective trial (1) and key retrospective studies				
Dose-modified oral chemo. (CWRU 2498/2009) [29]	49	78% (CR 58%/PR 20%)	MST 12.3 mos. (33% 1-yr)	Only published prospective treatment trial of AR-NHL in sub-Saharan Africa; conducted comparable HIV therapeutic era as ACTG 142 trial [45]; 6% treatment mortality rate.
Uganda Cancer Institute (NHL study/2011) [35]	154 (32% HIV+)	No response data provided or types of chemotherapy.	MST 61 days (13% 1-yr)	Largest retrospective study on NHL including HIV(-) and HIV(+) cases ever reported with treatment and outcome data. Only 60% had acceptable clinical staging.
Stellenbosch University (NHL study/2010) [19]	512 (4 HIV+)	Overall CR range 46–75% for all subtypes; chemotherapy regimens not reported.	MST 10 mos. (50% 1-yr)	Comprehensive retrospective study of spectrum lymphoproliferative disorders at a major private referral centre in Cape Town. Only 4 cases (<1%) were HIV(+). MST is for the 4 AR-NHL cases.
Uganda Cancer Institute (Pediatric BL study/2009) [34]	228 (31% HIV+)	36% CR HIV(+) 41% CR HIV(-)	MST 11.8 mos. HIV(+) Not reached HIV(-)	Comprehensive and largest retrospective study of pediatric BL in sub-Saharan Africa. No details on types of chemotherapy administered.
University of Nairobi (BL study/2001) [36]	796 with 29 adult BL (66% HIV+)	No response data reported or types of chemotherapy.	MST 15 wks.	Among earliest period prevalence and retrospective study that identified 3-fold increase in adult BL cases in the AIDS era. MST is for HIV(+) BL.
(B) United States Data—Select clinical trials				
Concurrent R-EPOCH versus sequential R-EPOCH (AMC 034/2010) [53]	48 concurrent 53 sequential	73% CR concurrent 55% CR sequential	2-yr OS 70% concurrent versus 67% sequential	Randomized phase II trial of concurrent versus sequential rituximab with EPOCH chemotherapy; the primary efficacy endpoint of CR achieved only for the concurrent arm.
R-CHOP versus CHOP (AMC 010/2005) [49]	150	58% CR R-CHOP 47% CR CHOP	139 wks. OS R-CHOP 110 wks. OS CHOP	Randomized trial among first to use rituximab; raised concern with higher infectious deaths on R-CHOP arm; not substantiated in future trials with rituximab.
Infusional CDE (ECOG E1494/2004) [48]	98	45% CR	2-yr OS 43%	Among largest studies of a highly active infusional regimen conducted during emergence of cART era.
Infusional EPOCH (NCI/2003) [47]	39	74% CR	63% OS at 53 mos.	Dose-adjusted (on basis of CD4+ lymphocyte count) chemotherapy regimen with interruption of cART amongst highest CR and survival reported at time.
LD and SD CHOP (AMC 005/2001) [46]	40 LD 23 SD	30% CR LD 48% CR SD	Not reported	Not randomized; 2 consecutive treatment arms established feasibility of concurrent chemotherapy with cART. Median duration of response 9mos. LD; not reached for SD CHOP.

Anticancer agents that are “generally” available in resource-limited settings in sub-Saharan Africa

TABLE 2

Formulary of cytotoxic chemotherapy and other agents used for the treatment of NHL and generally available in resource-limited settings in sub-Saharan Africa. There may be instances where agents are purchased or secured in the private setting (e.g., patients and/or private hospitals) but this falls outside the realities of access to and chemotherapy coverage that is available in large national referral medical centers or regional health centers (e.g., essentially public institutions) in most sub-Saharan Africa nations. Adopted from Orem et al. [22]

Bleomycin	Leucovorin
Cyclophosphamide	Methotrexate
Cytarabine	Nitrogen mustard *
Dacarbazine *	Prednisone
Dactinomycin	Procarbazine *
Daunorubicin *	Vinblastine *
Doxorubicin	Vincristine
Etoposide *	Vinorelbine **
Gemcitabine **	Colony-stimulating factors (CSFs) ***
Hydroxyurea *	Rituximab **

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(Notes: Supply may be variable;

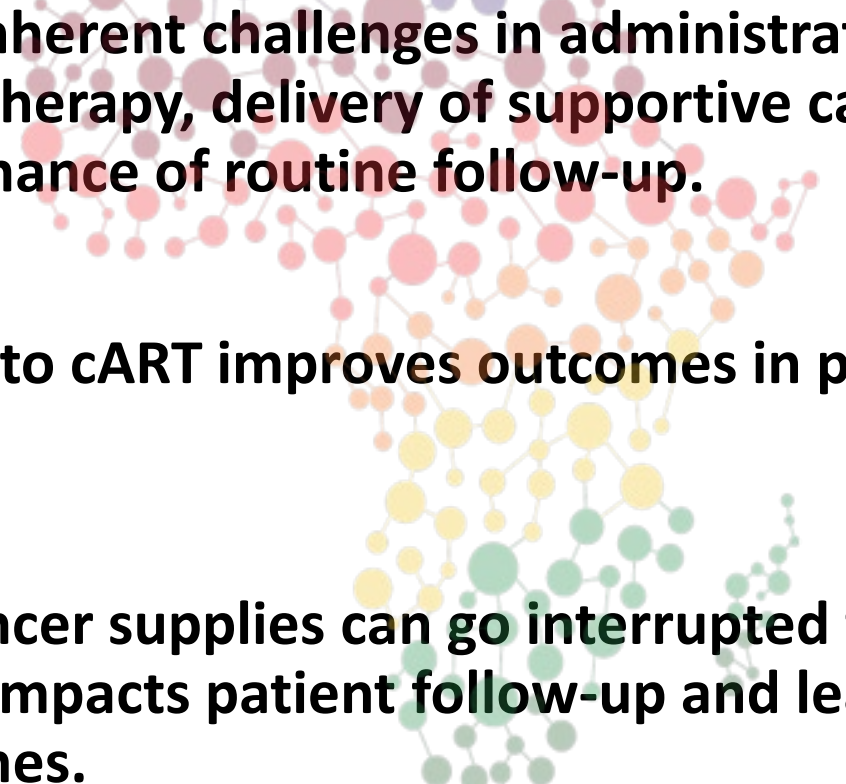
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generally not available;

unavailable.).

Discussion

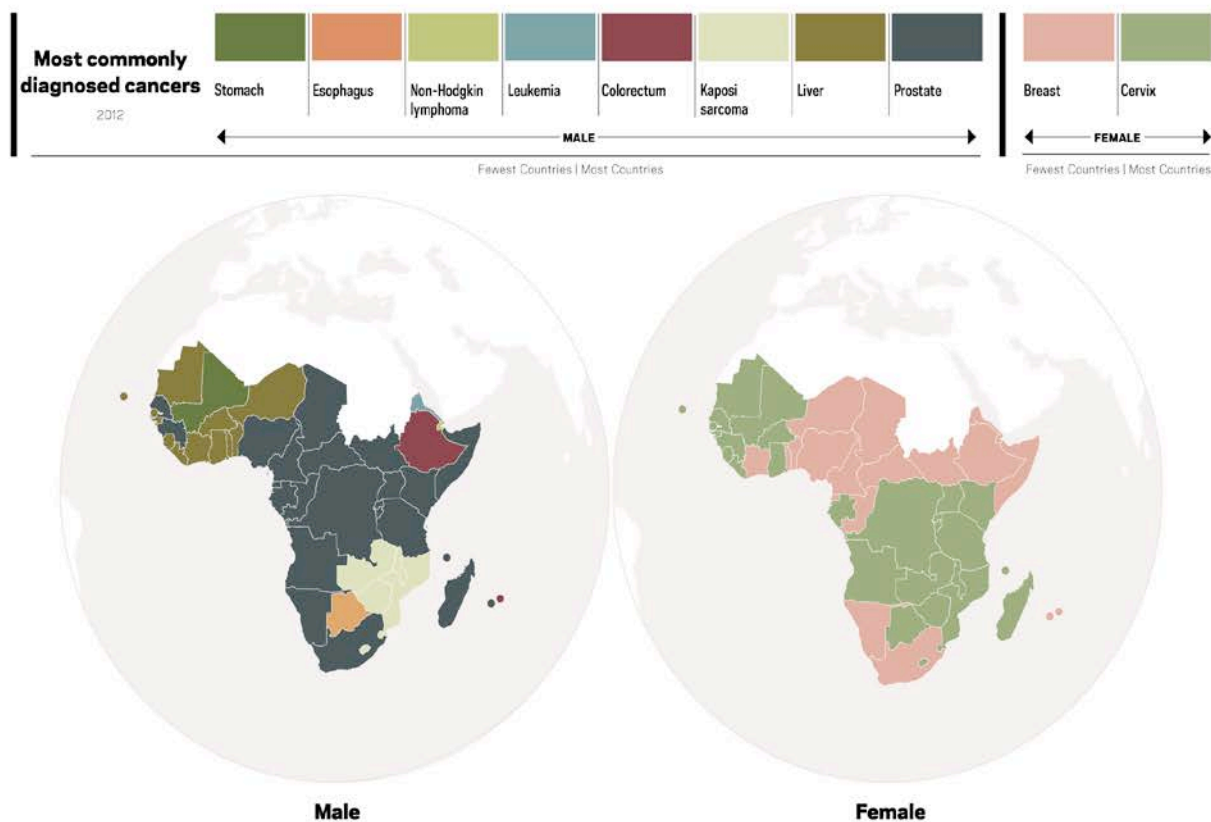
- In 2009 first prospective clinical trial of AR-NHL was reported from Kenya and Uganda utilizing dose-modified oral chemotherapy regimen.
 - Studies showed that dose modification of chemotherapy lessened myelotoxicity without compromising efficacy in the pre-cART era in the US, which led to dose modified oral regimens in sub-Saharan Africa.
- In 2011, a retrospective study (Bateganya et al.) reported clinical outcomes in AR-NHL from Uganda.
 - Median survival was 61 days, 32% were HIV+
 - Median survival among patients with HIV infection receiving ART was comparable to those without HIV infection.

Discussion (2)

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- **Great inherent challenges in administration of chemotherapy, delivery of supportive care, and performance of routine follow-up.**
 - **Access to cART improves outcomes in patients with AR-NHL.**
 - **Anticancer supplies can go interrupted for periods of time which impacts patient follow-up and leads to poor outcomes.**

The cancer profile varies across Sub-Saharan Africa, with infection-related cancers leading in many areas.

Most commonly diagnosed cancers in the region



A higher proportion of cancer cases are due to infection in lower income countries, particularly in Asia and Sub-Saharan Africa.

Fraction of new cancer cases attributable to infection (by region, 2008)

