Articles

Outcomes of patients with Kaposi's sarcoma who start antiretroviral therapy under routine programme conditions in Malawi

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SUMMARY AIDS-associated Kaposi's sarcoma (KS) is the most common AIDS-related malignancy in sub-Saharan Africa, with a generally unfavourable prognosis. We report on six-month and 12-month cohort treatment outcomes of human immunodeficiency virus (HIV)-positive KS patients and HIV-positive non-KS patients treated with antiretroviral therapy (ART) in public sector facilities in Malawi. Data were collected from standardized antiretroviral (ARV) patient master cards and ARV patient registers. Between July and September 2005, 7905 patients started ART-488 (6%) with a diagnosis of KS and 7417 with a non-KS diagnosis. Between January and March 2005, 4580 patients started ART-326 (7%) with a diagnosis of KS and 4254 with a non-KS diagnosis. At six-months and 12-months, significantly fewer KS patients were alive and significantly more had died or defaulted compared to non-KS patients. HIV-positive KS patients on ART in Malawi have worse outcomes than other patients on ART. Methods designed to improve these outcomes must be found.

Introduction

Endemic Kaposi's sarcoma (KS), a multifocal neoplasm involving predominately skin and mucous membranes, has been reported sporadically from sub-Saharan African countries for many years. However, with the advent of human immunodeficiency virus (HIV) infection, epidemic or AIDS-associated KS has become by far the most common form of the tumour and also the most common AIDS-related malignancy observed in clinical practice.[1] Treatment options in industrialized countries include systemic or combination chemotherapy (commonly used drugs being vincristine, vinblastine, bleomycin, doxorubicin and dacarbazine), interferon alfa and radiation therapy.[1] Even though none of these, in the absence of highly active antiretroviral therapy (ART), provides a cure for AIDS-associated KS,[2] they do allow significant palliation. Unfortunately, in most poorly resourced African countries these treatment modalities are not available and treatment for the most part has been confined to pain relief and to the treatment of secondary infections.

The advent of ART has changed the natural history of KS in HIV-positive individuals. Response rates of KS to ART of up to 90% have been observed in some studies, with complete remission in patients with good immunological responses, in patients with no systemic symptoms and those where lesions are confined to the skin.[3,4] Disease-free survival of HIV-positive patients started on ART due to KS has also significantly improved.[5] Until two or three years ago, ART was only available in industrialized countries. However, with the World Health Organization's (WHO) '3 by 5' initiative, many resource-poor countries started scaling up ART for their HIV-infected communities. By December 2005, over 800,000 patients had been commenced on ART in Africa.[6] While the availability of ART has renewed the enthusiasm for treating KS, to our knowledge there is a scarcity of published information about outcomes for KS patients in Africa who have been treated with ART under routine programme conditions.

Every three months the HIV unit of the Ministry of Health, Malawi, and its partners conduct supervisory and monitoring visits to all sites in the country that are delivering ART in the public sector. Data are collected on the numbers and characteristics of patients starting ART and their outcomes. We used these structured visits to obtain additional information on outcomes of KS patients who had been started on ART, and compared their outcomes with those for non-KS patients on ART.

Methods

Background

Scaling up and delivering ART in Malawi The process and nature of ART scale-up in Malawi has already been described,[7,8] and only the main elements will be described below. A standardized, structured approach is used which includes

- a focus on one generic, fixed-dose combination treatment with stavudine, lamivudine and nevirapine to be delivered free of charge to HIV-positive eligible patients;

- a standardized system of registration, monitoring and reporting of cases and outcomes and
- quarterly supervision and evaluation of all ART sites.

Two alternative first-line regimens (for any serious side effects of ART drugs) and one second-line regimen (for ART drug failure) have been placed in central hospitals and two district hospitals. A referral system has also been set up to enable patients in need to access the appropriate therapy.

Facilities in the public health sector have been selected in a phased approach for antiretroviral (ARV) scale-up and now, after training the staff and formally accrediting the sites, they have started to deliver ART. By March 2006, 66 sites were delivering ART using the national standardized systems.

When a patient is found to be HIV-positive, referral is made to the ARV clinic for clinical staging. If the patient is found to be eligible for ART (assessed as being WHO Clinical Stage 3 or 4 or with a CD4-lymphocyte count $<200/mm^3$), he/she is asked to attend, accompanied by a guardian, for a group counselling/briefing session conducted by one of the ARV clinic staff in order to be given information about ART. The patient is then asked to return a few days to a week later for individual counselling and for the start of ART. Patients are then followed up, first at two weeks and thereafter at four-week intervals, with assessments and drugs distributed from the ARV clinic.

Management of patients with KS Patients with KS will be HIV tested and counselled; those who are HIV-positive will be eligible for ART because they are in WHO clinical stage 4 category.[9] For patients with bulky tumours or visceral involvement, the usual clinical practice in Malawi is to treat them with vincristine, administered as an intravenous dose of 2 mg once a week, for two to three weeks before commencing ART. They must then complete a total of six weeks of vincristine.

Monitoring and evaluation for ART During the monthly ART monitoring visits, vital data is recorded using standardized monitoring tools such as the ARV patient master cards and ARV register.[7] Standardized treatment outcomes are recorded every month on the master cards and updated in the ARV register. Every three months a quarterly cohort analysis is performed on the most recent three-month cohort of patients started on ART and the cumulative cohort of all patients started on therapy. Facilities record case finding characteristics and treatment outcomes at a set point in time; these are checked and collated by the HIV unit and its partners during the quarterly supervisory visits.[10]

Data collection

By the end of March 2006, there were 66 sites in the public sector delivering ART to patients. They were all visited between April and June 2006. Data for quarterly and cumulative cohort analyses were collected into a structured proforma, and then entered into an Excel spread sheet for collation. Sixty sites had started patients on ART between 1 July and 30 September 2005, and their treatment outcomes were censored on 31 March 2006 to provide a so-called six-month cohort survival analysis: in effect this means an analysis of patient outcomes six to nine months after starting ART. Between 1 January and 31 March 2005 there were 35 sites that had started patients on ART. Their treatment outcomes were also censored on 31 March 2006 to provide a so-called 12-month cohort survival analysis: this, in effect, means an analysis of patient outcomes 12–15 months after starting ART. In addition, during these same two quarterly periods patients registered as having KS were identified from the ARV patient master cards, and their outcomes were censored on 31 March 2006 to provide a six-month and 12-month survival analysis for KS patients.

Analysis

Six-month and 12-month survival outcomes were performed for patients with KS. The numbers of KS patients and their outcome data were subtracted from all patients started on ART during the same time periods, and a calculation was made for survival outcomes for non-KS patients. Differences in treatment outcomes between groups were compared using the χ^2-test. Relative risks (RR) and 95% confidence intervals (CI) were obtained, with differences at the level of 0.05 being regarded as significant.

Results

Between 1 July and 30 September 2005, 7905 patients started ART-488 (6%) with a diagnosis of KS and 7417 with another non-KS diagnosis. The six-month cohort outcomes of KS and non-KS patients censored on 31 March 2006 are shown in Table 1. At six months, significantly fewer KS patients

Table 1 Six-month and 12-month outcomes in quarterly cohorts of Kaposi's sarcoma (KS) patients and non-KS patients started on antiretroviral treatment (ART) in Malawi in 2005, with outcomes censored on 31 March 2006

Treatment outcome parameter	*KS patients*	*Non-KS patients*	*RR (95% CI)*[a]	*P-value*
Six-month treatment outcomes				
Number started on ART	488	7417		
Number (%) alive[b]	277 (57)	5426 (73)	0.78 (0.72–0.84)	<0.001
Number (%) dead[c]	111 (23)	861 (12)	1.96 (1.64–2.33)	<0.001
Number (%) defaulted[d]	65 (13)	589 (8)	1.68 (1.32–2.13)	<0.001
Number (%) stopped[e]	5 (1)	54 (1)	1.41 (0.57–3.50)	NS
Number (%) transferred[f]	30 (6)	487 (6)	0.94 (0.66–1.34)	NS
12-month treatment outcomes				
Number started on ART	326	4254		
Number (%) alive[b]	172 (53)	2801 (66)	0.80 (0.72–0.89)	<0.001
Number (%) dead[c]	71 (22)	509 (12)	1.82 (1.46–2.27)	<0.001
Number (%) defaulted[d]	48 (15)	462 (11)	1.36 (1.03–1.79)	<0.05
Number (%) stopped[e]	6 (2)	46 (1)	1.70 (0.73–3.96)	NS
Number (%) transferred[f]	29 (8)	436 (10)	0.87 (0.61–1.24)	NS

[a]RR between KS patients and non-KS patients
[b]Alive and on ART at the facility where the patient registered for therapy
[c]Died for any reason
[d]No attendance at the antiretroviral clinic for three months or longer for no known reason
[e]Stopped treatment for any reason
[f]Permanently transferred out to another treatment facility
CI, confidence interval; NS, not significant; RR, relative risks

were alive and significantly more had died or defaulted than the non-KS patients.

Between 1 January and 31 March 2005, 4580 patients started ART-326 (7%) with a diagnosis of KS and 4254 with another non-KS diagnosis. The 12-month cohort outcomes of KS and non-KS patients censored on 31 March 2006 are also shown in Table 1. At 12 months, significantly fewer KS patients were alive and significantly more had died or defaulted compared to non-KS patients.

Discussion

In both quarters, between 5–10% of patients starting ART were placed on treatment because they had KS. The proportion of KS patients alive at six-months and 12-months was significantly lower compared to other non-KS patients: this was due to higher death rates and default rates. Default means loss to follow-up, and unpublished data suggest that a large percentage of defaulters are, in fact, patients who have died. Despite these inferior results, over half the patients with KS and on ART were still alive one year after commencing treatment.

This was an operational study conducted within the routine system and therefore has all the limitations of this type of research. Data were not collected on the demographic characteristics of patients, the extent of disease (which has been shown to influence prognosis),[3] or HIV – or drug-related morbidity or causes of death. We also have no information about how many KS patients received their vincristine. There was a general shortage of the drug in country during the latter half of 2005, with 35% of ART facilities having completely run out of stock of vincristine between July and September 2005 (source: HIV Unit, Ministry of Health, Malawi). However, the strengths of the study were that it was countrywide, the routine systems for monitoring patients using master cards and registers are robust and regularly checked by supervising teams, and we believe that the results are reliable and representative. The use of six-month and 12-month quarterly cohort analysis is now well established and enables survival analyses to be carried out as part of the routine system. For busy ART facilities and supervising teams with scarce human resources, individual patient survival outcomes are too time-consuming to carry out. Cohort survival analysis, however, is quick and reliable provided the registers are regularly updated.

There are many aspects that require further assessment. In particular, treatment outcomes in the routine setting need to be analysed in relation to (1) the staging of AIDS-KS, particularly bulk of the disease, pulmonary involvement and systemic illness and (2) the usefulness of prior and continuation treatment with cytotoxic chemotherapy with either vincristine or bleomycin (the latter given by intramuscular injection which is easier to administer). However, in resource-poor countries there are always going to be difficulties in procuring and accessing cytotoxic drugs. It is therefore necessary to identify KS patients earlier in the disease when ART on its own is likely to provide significant benefits in terms of reducing the bulk of disease and improving long-term survival.

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Current investigations and treatment of Burkitt's lymphoma in Africa

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SUMMARY We reviewed the scientific literature on Burkitt's lymphoma (BL) in Africa in order to provide information on the current status of clinical care and the existing research challenges. BL epidemiology led to the discovery of the Epstein Barr virus, an important cause of several viral illnesses and malignancies. The incidence of BL