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Review

A review of the efficacy and outcomes studies of currently approved chemotherapy treatments for advanced AIDS-Kaposi's sarcoma

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ABSTRACT

Background: Acquired Immune Deficiency Syndrome (AIDS)—related Kaposi's sarcoma (KS) is a rare aggressive tumor. The benefits of drug therapy are established by clinical trials but it has been a challenge to draw comparisons between the different advanced AIDS-KS pharmacotherapy available. This review aims to evaluate the currently approved chemotherapy drugs for the treatment of AIDS-related advanced KS as well as the economic burden and impact on the quality of life of patients.
Material and methods: Relevant articles were identified through a systematic review of the literature via a search of the National Center for Biotechnology Information (NCBI) PubMed database and the Internet (clinicaltrials.gov) using relevant medical subject heading (MESH) terms.
Results: A total of 7 phase II and 4 phase III trials of liposomal anthracyclines (liposomal doxorubicin [PLD] and/or liposomal daunorubicin [DNX]) were identified. An evaluation of the trials comparing PLD to a competitor showed statistical difference p;0.01. DNX phase III trials were also evaluated and showed no statistical differences ($p = 0.64$). For paclitaxel, 6 clinical trials were selected (5 phase II and 1 phase III); however heterogeneity was not evaluated. 4 cost-effectiveness studies were compared and 3 concluded that PLD is more cost-effective than the competitor. 4 quality of life studies were analyzed.
Conclusion: AIDS-KS impacts the patient's life physical, emotional and economic well being. In this work we compared studies of liposomal anthracyclines, still; further research among all the approved drugs for KS is warranted to evaluate efficacy as well as its economic burden worldwide.

1. Introduction

Kaposi's sarcoma (KS) is a rare tumor caused by the human-herpes virus (HHV-8) and was first described in 1872 by the Hungarian physician Moriz Kaposi as a "sarcoma idiopathicum multiplex haemorrhagicum" [1,2]. Kaposi's sarcoma comprehends four types of neoplasm subgroups: classic, endemic, transplant-associated and epidemic [2]. The latter, characterized by human immunodeficiency virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) infection, became a health concern with the advent and pandemic of this infection in the 1980s. Treatment is often done for cosmetic reasons (reduction of lesions in the body) and to reduce symptoms associated with the disease. There are five drugs approved by the FDA for the treatment of lesions in different stages of KS. For the early stage cases interferon-alfa and alitretinoin gel 0.1% are the treatment of choice. For advanced disease, liposomal anthracyclines [doxorubicin (PLD) or daunorubicin (DNX)] are the first-line treatment recommendation. In the case of anthracyclines-resistant patients, paclitaxel is the approved second-line therapy.

With the introduction of highly antiretroviral therapy (HAART) in 1996, and a more strict definition of AIDS by the Centers for Disease Control and Prevention (CDC), the incidence of this cancer has declined significantly ($2/10^5$ age-adjusted incidence rate now compared to $17.1/10^5$ age-adjusted incidence rate in the peak of the AIDS epidemic) still, approximately 15% of AIDS patients develop KS [2,3]. HAART acts by improving the patient's immune system rather than having an antiviral activity against HHV-8, involved in this disease. Hence, some researchers believe that the use of HAART is only delaying the progression of KS, and in the future we may face a significant increase on KS incidence [4]. Nonetheless, the use of HAART in patients with AIDS-KS has led to self-healing causing spontaneous resolution of KS lesions [4].

Despite the low incidence of AIDS-KS in the US, there is still no cure for AIDS-KS; thus it is important to study ways to improve treatment and reduce morbidity in patients as well as having more cost-effective drugs that provide affordable treatments [5]. The goal of this review is to assess the efficacy of the currently Food and Drug Administration (FDA)-approved treatments for advanced AIDS-KS and evaluate health economic studies related to this condition in

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Table 1
Overall response rates of Kaposi's sarcoma in human immunodeficiency virus immunodeficient patients reported on Phase II clinical trials.

Author, year	Patients	PLD	DNX	Paclitaxel
Stebbing [19], 2003	17			71% (95%CI 60–81%)
Tulpule [20], 2002	107			56%(95%CI 46–66%)
Hengge [10], 2001	52	75%		
Gill [17], 1999	56			59% (95%CI 45–72%)
Newell [11], 1998	20	55%		
Tulpule [12], 1998	53		75% [a]	
Welles [22], 1998	28			71%(95%CI 51–87%)
Goebel [8], 1995	238	80.7% (95%CI 76–86%)		
Harrison [9], 1995	34	73.5%		
Gill [14], 1995	40		55%	
Girard [7], 1995	30		73% (95%CI 54–92%)	
Saville [18], 1995	20			65%(95%CI 41–85%)

Note: PLD: liposomal doxorubicin; DNX: liposomal daunorubicin.
[a] Pulmonary response.

order to summarize cost-effectiveness, as well as measuring the impact of the quality of life and the burden of this disease among HIV positive patients.

2. Methods

We searched PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) of the National Center for Biotechnology Information (NCBI) and clinicaltrials.gov for publications focused on the different treatments for advanced AIDS-KS. The search was conducted using the medical subject heading (MESH) terms Kaposi's sarcoma, pegylated liposomal doxorubicin, paclitaxel, AIDS-related opportunistic infections, quality of life and costs and cost analysis. The results of the literature search presented in the paper include review articles, randomized clinical trials (phases II and III), costs-effectiveness and quality of life studies. Response rates reported follow the AIDS Clinical Trial Group (ACTG) criteria. Eligible patient population included adults (males and females) diagnosed with AIDS-related KS in advanced stage and receiving any of the FDA-approved chemotherapeutic treatments for KS (liposomal anthracyclines or paclitaxel). Also, articles written in a language other than English were excluded from this review, though; the search was not restricted to any specific country. The time span considered for this review was 20 years (1990–2010).

2.1. Statistical analysis

We used the Chi-square test to assess the heterogeneity of the results of different randomized phase III trials.

2.2. Articles

For this analysis, we selected 7 phase II clinical trials of liposomal anthracyclines [6–12] and 4 phase III trials comparing the drugs among anthracyclines or to a standard treatment [13–16]. For paclitaxel, 6 clinical trials were evaluated [17–22]. Only 4 cost-effectiveness studies of drugs used for AIDS-KS were available, all comparing PLD to another regimen [23–26], two of those were independent and the other two were sponsored by Schering Plough Corporation and the National Cancer Institute, respectively [24,26]. At last, 4 quality of life studies were described using patient's preferences [8,20,27,28].

Table 2
Randomized phase III trials of chemotherapeutic drugs for Kaposi's sarcoma treatment.

Author, year, country	Regimen	Patients	Median cycles	Results
Gill [14], 1996, USA	DNX (40 mg/m^2) vs ABV every 2 weeks	227 total	8 cycles DNX	ORR: 25% (DNX) vs 28% (ABV)
		116 DNX arm and 111 ABV	7 cycles ABV	AE: less alopecia and neuropathy in DNX arm
Northfelt [15], 1998, USA	PLD (20 mg/m^2) vs ABV every 2 weeks	258 total	5.2 ± 1.4 (SD) cycles for PLD	ORR: 46% (PLD) vs 25% (ABV)
		133 PLD arm and 125 ABV arm	3.8 ± 1.9 (SD) for ABV	AE: less leucopenia, alopecia, vomiting and nausea in the PLD arm.
Stewart [16], 1998, UK and Germany	PLD (20 mg/m^2) vs BV every 3 weeks	241 total	6 cycles	ORR: 59% (PLD) vs 23% (BV)
		121 PLD arm and 120 in the BV arm		AE: less neuropathy in the PLD arm and more neuropenia.
Cooley [13], 2007, USA	PLD (20 mg/m^2) vs DNX (40 mg/m^2) every 2 weeks	79 total	6 cycles	ORR: 80% (PLD) vs 63.2% (DNX)
		60 PLD arm and 19 DNX (3:1)[a]		AE: neutropenia (30%), nausea (28.3%), and asthenia (16.7%) associated with PLD treatment
Von Roenn [21] 2007, USA and Cianfrocca [31], 2010, USA	Paclitaxel (100 mg/m^2) vs PLD (20 mg/m^2)	89 total		ORR: 57%(Paclitaxel) vs 46% (PLD)
		43 Paclitaxel arm and 46 PLD		AE: no statistical difference in toxicity Trials was early terminated due to poor accrual

Note: PLD: liposomal doxorubicin; DNX: liposomal daunorubicin; ABV: doxorubicin, bleomicin and vincristine; BV: bleomicin and vincristine. ORR: overall response rate; AE: adverse event; SD: standard deviation.
[a] Patients were randomized in a proportion 3:1.