Pegylated liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma

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Abstract: Kaposi's sarcoma is a vascular tumor of skin and viscera first described in 1872. Prior to the 1980s, this disease was rarely seen in the Western world, but was quite prevalent in Sub-Saharan African countries. Since the onset of the HIV pandemic in the 1980s, the incidence of Kaposi's sarcoma has increased markedly in Africa and continues to be a significant problem in association with AIDS in Western countries. Many therapies have been demonstrated to be effective in the treatment of HIV-related Kaposi's sarcoma, including alitretinoin gel, interferon alpha, and various forms of cytotoxic chemotherapy. Antiretroviral therapy combined with cytotoxic agents has yielded significantly greater efficacy than chemotherapy alone. However, as reviewed in this report, pegylated liposomal doxorubicin has been established as the treatment of choice for patients with AIDS-associated Kaposi's sarcoma in Western countries. Compelling preclinical and clinical evidence, reviewed herein, has demonstrated that the nanoparticle (pegylated liposome) delivery system of this formulation leads to greater tumor localization of doxorubicin and consequent improved efficacy, as well as reduced toxicity.

Keywords: liposomal doxorubicin, pegylated liposomal doxorubicin, Kaposi's sarcoma, liposomal daunorubicin, liposomal anthracyclinces

Introduction

Kaposi's sarcoma (KS) is the most common malignancy seen in patients with human immunodeficiency virus infection, occasionally as the initial manifestation acquired immunodeficiency syndrome (AIDS) (Wang et al 1995). Prior to the AIDS epidemic, KS was uncommon, occurring primarily in men in Africa, the Mediterranean area, or Eastern Europe (Mitsuyasu 2000). Although it was an exceedingly common complication of AIDS in western countries in the 1980s at the onset of the epidemic, in the 1990s the incidence of AIDS-related KS (AIDS-KS) in developed countries decreased dramatically; between 1990 and 1997, that decline was 10% per year. An additional decline in the incidence of AIDS-KS occurred in association with widespread implementation of highly active antiretroviral therapy (HAART) in the late 1990s. Also, it has been speculated that safer sexual practices among homosexual men may have led to reduced transmission of human herpesvirus-8 (HHV-8), the virus associated with all forms of KS, and that the introduction of more effective antiretroviral treatments with associated reduction in immunodeficiency may also have resulted in a more effective immune response to HHV-8. Any or all of these factors could account for the observed decline in incidence of AIDS-KS over the course of the epidemic.

Nevertheless, AIDS-KS continues to be diagnosed among HIV-infected persons. Control of HIV infection is not uniformly achieved with HAART, either because of drug resistance and/or as a result of poor adherence to prescribed drug regimens. Additionally, some patients continue to develop AIDS-KS despite effective HIV suppression. Furthermore, rates of AIDS-KS continue to rise in parts of Africa where rates of both HIV and HHV-8 infection are high and HIV treatment is not widely available.

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Clinical presentation of AID-KS

AIDS-KS is a multifocal, systemic disease that usually first appears as pink, red, purple, or brownish-black nodules, macules, patches, or plaques on the skin or, less often, on the oral mucosa (Wang et al 1995). In the setting of HIV infection, AIDS-KS lesions often occur on the upper body, especially the head and neck. Disease confined to the lower extremities is more common in non-HIV-associated KS (Misuyasu 2000). Oral lesions have reportedly accounted for 22% of the sites of initial presentation in AIDS-KS. Lesions of AIDS-KS may develop in the lungs, gastrointestinal tract, and lymph nodes and have also been described in the gallbladder, on the mucosa of the vocal cords and conjunctiva, genitalia, liver, spleen, heart, bone, thyroid gland, and/or bone marrow (Wang et al 1995). Depending on their location and size, AIDS-KS lesions may be disfiguring and can cause edema, pain, gastrointestinal bleeding, and tooth loss, and can lead to nutritional deficiencies and disfigurement with consequent social isolation. Moreover, lesions in critical sites can interfere with eating, speaking, breathing, and sometimes produce fatal consequences (Peters et al 1991; Wang et al 1995). The course of the disease varies from development of single or a few indolent lesions with minimal progression over time, to aggressive, debilitating, widespread disease with severe complications emerging within a short time (Wang et al 1995; Krown 2004).

Rationale for use of liposomal anthracyclines in treatment of AIDS-KS

Several liposomal anthracycline products have been investigated for the treatment of AIDS-KS. In particular, a polyethylene glycol-coated ("pegylated") liposomal product with trade names Doxil® or Caelyx® (doxorubicin HCl liposome injection [PLD]; the former distributed in the US by Tibotec Therapeutics, Division of Ortho Biotech Products, LP, Bridgewater, NJ; the latter distributed outside the US by Schering-Plough Corp.), received accelerated approval from the United States Food and Drug Administration (US FDA) in November 1995 for treatment of patients with AIDS-KS whose disease either had progressed on prior combination chemotherapy or who were intolerant of such therapy (Doxil 2001). In April 1996, the non-pegylated liposomal product, DaunoXome® (DNX, daunorubicin citrate liposome; Gilead Sciences, Foster City, CA) was approved as treatment of AIDS-KS for which no prior chemotherapy had been administered ("first-line" treatment) (DaunoXome 1996). Results of a phase II trial in AIDS-KS patients were also reported for a non-pegylated formulation of liposomal doxorubicin, Myocet® (liposome-encapsulated doxorubicin citrate complex; Medeus Pharma, Stevenage, Herts UK) (Cheung et al 1999), but this agent is not approved for treatment of AIDS-KS in the US.

Encapsulation of conventional doxorubicin within liposomes was expected to preferentially distribute drug into tumors with "leaky" blood vessels, a condition which it was believed would facilitate the extravasation of liposomes into tumor stroma (Allen and Martin 2004). Because AIDS-KS lesions contain dilated vascular spaces filled with extravasated erythrocytes, good drug uptake due to similar extravasation of liposomes was anticipated. "Pegylation" of liposomes was expected to offer advantage over conventional liposomes by preventing early clearance of circulating liposomes by macrophages of the reticuloendothelial system. This would theoretically lead to longer circulation time for the liposomes and thereby enhance their opportunity to traverse tumor vasculature where extravasation could occur.

In vitro studies demonstrated the antitumor activity of conventional doxorubicin in KS-derived cell cultures (Logan et al 1991). Other in vitro studies showed that exposure to PLD inhibited the proliferation of KS-derived cells to a greater extent than the proliferation of endothelial cells, monocytes, and smooth muscle cells (Sturzl et al 1994). It was also shown that PLD increased the expression of monocyte chemoattractant protein-1 in KS cells, a substance believed to lead to increased migration of monocytes into the tumor (Sturzl et al 1994). Before initiation of clinical studies, it was shown in animal models of KS that PLD was preferentially taken up into tumor tissue (Huang et al 1993). Using a model of KS dermal lesions in transgenic mice bearing the HIV *tat* gene (Vogel et al 1998; Huang et al 1993), pegylated liposomes were shown to extravasate into the interstitial spaces between spindle-shaped KS cells. Liposomes were found predominantly within the lesion in the region adjacent to the epidermis, with dense concentrations around abnormal blood vessels. In addition, electron microscopy showed that some macrophages and spindle cells had ingested intact liposomes. Skin biopsies of patients under treatment with PLD provided additional evidence for the preferential tumor uptake observed in animal models (Vail et al 2004). When encapsulated in a pegylated liposome, doxorubicin concentrations in KS lesions reached 10–20 times those in normal skin (Northfelt et al 1995). In addition, it was shown that more doxorubicin was delivered to AIDS-KS lesions when administered as PLD than as conventional doxorubicin. Kaposi's lesions from 18 patients were biopsied 72 hours after intravenous injection of either PLD

or conventional doxorubicin (Northfelt et al 1996). Regardless of the dose, tissue levels of doxorubicin were approximately 5–11 times higher in the AIDS-KS lesions of patients treated with PLD compared with AIDS-KS lesions in patients given comparable doses of conventional doxorubicin.

Efficacy of liposomal anthracyclines in clinical trials of treatment for AIDS-KS

Results of phase I/II trials of PLD in relatively unselected cohorts of patients with AIDS-KS demonstrated overall response rates (complete and partial response [CR + PR]) ranging from 38% to 100% (Sturzl et al 1994; Hengge et al 1993, 2001; Simpson et al 1993; Bogner et al 1994; James et al 1994; Wagner et al 1994; Bergin et al 1995; Harrison et al 1995; Goebel et al 1996; Northfelt et al 1997; Grunaug et al 1998; Newell et al 1998; Nuncez et al 2001). To illustrate these findings we will focus on the trial reported by Northfelt et al (1997) (Table 1), which provided the data that led to initial approval of PLD by the United States Food and Drug Administration (US FDA). It was limited to patients who had experienced disease progression or intolerable toxicities during treatment with the combination of doxorubicin, bleomycin, and vincristine (ABV) or the combination of bleomycin and vincristine (BV) chemotherapy. The 53 patients enrolled in this trial received 20 mg/m^2 of PLD intravenously once every 3 weeks; 19 patients (36%) achieved PRs and one achieved a complete clinical response. Among those who had previously experienced disease progression when receiving a conventional doxorubicin-containing regimen (eg, ABV rather than BV), the PR rate was 32%. Median duration of response and time to treatment failure in all patients was 128 and 134 days, respectively. Of the 53 patients, 48 had raised indicator lesions at baseline; a complete flattening of these lesions occurred in 48% of these patients and 68% achieved partial or complete responses. Forty-eight of the patients had red or purple indicator lesions at baseline; in 56% of these patients the lesions changed to a less noticeable color, and 82% of these patients achieved partial or complete responses. Among the 23 patients with edema at study entry, study therapy reduced edema in 83%, and 100% of those achieved PR or CR. Of the 22 patients with pain at baseline, 45% (70% of whom attained PR or CR) had pain reduction. These apparent benefits of PLD did not result in PR or CR in some patients because they failed to fulfill some other qualification for response, such as no progression at other sites.

Table 1 Efficacy of pegylated-liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma after failure of standard chemotherapy (Northfelt et al 1997)

Best response	All patients (n = 53)	Doxorubicin failure[a] (n = 28)
Complete clinical	1 (2%)	0
Partial	19 (36%)	9 (32%)
Stable	19 (36%)	14 (50%)
Progression	14 (26%)	5 (18%)
Median time (days) to PR	109	109
Median duration (days) of PR	128	127
Median time (days) to treatment Failure	134	148

[a]Patients whose AIDS-KS progressed on a combination regimen containing doxorubicin.

Although not addressed specifically in the study described above, other observations demonstrated that PLD could be effective in relieving symptoms and possibly prolonging survival of patients with pulmonary AIDS-KS. In a retrospective analysis of 20 patients, including nine who had received prior chemotherapy, 11 of 16 patients whose tumors could be evaluated had improved findings on chest radiography, and the average arterial partial pressure of oxygen (pO_2) for all patients rose to 76 from 55.5 mmHg ($p < 0.01$). Dyspnea and/or cough resolved in 12 of 16 patients who had been symptomatic before treatment (Grunaug et al 1998).

The evidence supporting the use of PLD alone as first-line therapy is derived from two randomized trials in which patients on the control arm received either ABV or BV (Table 2) (Stewart et al 1998; Northfelt et al 1998). In the trial conducted by Stewart et al (1998) 241 patients who had received no prior cytotoxic chemotherapy were randomized to receive either PLD 20 mg/m^2 or BV (bleomycin 15 mg/m^2 and vincristine 1.4 mg/m^2). Both regimens were administered intravenously every 3 weeks for six cycles. Overall best response (CR plus PR) was significantly higher with PLD (58.7% vs 23.3%; $p < 0.001$), as was end-of-treatment response (38.8% vs 14.2%; $p < 0.001$). The end-of-treatment response reflected the patient's status at the time further therapy was discontinued; the response designation was scored within 21 days of the last dose of therapy and must have been sustained for at least 4 weeks. The average time to response was 49 days with PLD vs 57 days with BV. The mean duration of response was similar for the groups (160 days with PLD vs 157 days with BV). PLD produced significantly greater improvements in lesion thickness, nodularity, edema, color,

Table 2 Response rates in randomized trials comparing a liposomal anthracycline with ABV or BV[a,b]

	Stewart et al 1998			Northfelt et al 1998		
	PLD (Doxil) (n = 121)	BV (n = 120)	P value	PLD (Doxil) (n = 133)	ABV (n = 125)	P value
CR, %	6	1	<0.001	1	0	NS
PR, %	53	45	<0.001	45	25	<0.001
CR + PR, % (95% CI)	59 (50–67)	23 (16–31)		46 (37–54)	25 (17–32)	
Stable disease, %	38	68		53	67	
Progressive disease, %	0	4		2	8	
Not assessable, %	3	5		0	0	

[a]Best response during treatment.

[b]Partial response defined as absence of new cutaneous or oral lesions, new visceral sites of involvement, or the appearance or worsening or tumor-associated edema or effusions plus at least one of the following: a 50% decrease in the sum of the products of the skin lesions, complete flattening of greater than 50% of all previously raised skin lesions, a 50% decrease in the sum of the products of the largest perpendicular diameters of prospectively selected indicator skin lesions, or the patient met the criteria for Complete Clinical Response, except that residual tumor-associated edema or effusion was present. The response was required to persist for at least 4 weeks.

Abbreviations: ABV, doxorubicin, bleomycin, vincristine; BV, bleomycin, vincristine; CR, complete response; PR, partial response; NS, not significant.

pain, and size than did BV. Among those treated with PLD, the incidence of pulmonary symptoms (dyspnea, cough, chest pain, or effusion) dropped from 23.1% to 10.6% (p = 0.002), while for those on the BV regimen, pulmonary symptoms decreased from 24.4% to 20.2% (p = 0.25). The incidence of gastrointestinal symptoms related to AIDS-KS (bleeding, early satiety, or dysphagia) decreased from 16.3% at baseline to 3.8% with PLD treatment (p < 0.001), and from 17% to 9.4% (p = 0.06) with BV treatment. Mortality was similar in the two groups: 15.7% with PLD vs 14.2% with BV, with a mean time to death of 239 days versus 160 days, respectively. Only three of the deaths were caused by KS and none was attributed to the treatments studied. This study, as well as most of the others trials described here, was conducted before the introduction of HAART. Because survival of AIDS-KS patients is determined primarily by opportunistic infections and other non-KS complications of AIDS, the durations of survival in these studies is shorter than might be expected today with availability of more effective treatment of the underlying disease.

In the second randomized trial of first-line therapy with PLD for AIDS-KS (Northfelt et al 1998), also performed before the introduction of HAART, 258 patients with no prior chemotherapy were randomized to receive either PLD (20 mg/m^2) or ABV (conventional doxorubicin 20 mg/m^2, bleomycin 10 mg/m^2, and vincristine 1 mg), administered every 2 weeks. The overall response was significantly better with PLD than with ABV (45.9% vs 24.8%; p < 0.001) (Table 2). The time to response was again shorter with PLD (median, 39 days vs 50 days with ABV; p = 0.014). Compared with PLD, more than three times as many patients discontinued ABV because of an adverse event (37% vs 11%). PLD-treated patients remained on treatment longer either because it was well tolerated or because they responded to treatment. More rapid dropout of patients in the ABV treatment group might have influenced cumulative response rates, but the study did not examine this possibility. Significant differences between the treatments favored PLD in the frequency with which lesions decreased in size, indicator lesions flattened, lesion color returned closer to that of normal skin, pulmonary dysfunction improved, pain decreased, head and limb mobility improved, exercise tolerance increased, sleep disturbances decreased, and a sense of social well-being increased. The treatments showed no significant differences in reduction of lesion edema or pain, or patients' ability to walk or wear clothing more easily. Neither the median duration of response (PLD, 90 days; ABV, 92 days; p = 0.234) nor the median overall survival (both groups, 160 days differed between treatment groups.

Patients enrolled in the trial comparing PLD with ABV (Northfelt et al 1998) were asked to complete a 30-item AIDS-related health-related quality of life questionnaire before treatment (baseline), every 2 weeks during treatment, and approximately 21 days post-treatment (Osoba et al 2002). Twenty-two items were assessed within 9 domains: general health, pain, social functioning, and overall quality of life (1 item each); mental health (5 items); energy/fatigue (4 items); health distress (4 items); and cognitive functioning (4 items). Scores at baseline and end of treatment were transformed to a scale from 0 to 100, with higher scores indicating better health.

In each of the domains there was an improvement in health-related quality of life associated with PLD treatment, and six of these nine changes were statistically significant (Table 3) (Osoba et al 2001). In contrast, ABV treatment resulted in improved health-related quality of life in only two domains and in worsened health-related quality of life in three domains, two of which were significantly reduced.

Table 3 Changes in health-related quality-of-life parameters in patients with Kaposi's sarcoma

Domain	PLD (Doxil) (n = 118)			ABV (n = 114)			
	No. of patients	Change from baseline[a]	P value[b]	No. of patients	Change from baseline[a]	P value[b]	P value between groups[c]
General health	91	3.3	NS	85	–3.3	0.05	0.02
Pain	73	8.3	0.01	74	0	NS	0.01
Cognitive functioning	70	5.0	0.008	61	0	NS	NS
Mental health	93	3.3	0.03	89	0	NS	NS
Overall quality of life	90	4.0	0.05	85	–2.0	NS	NS
Social functioning	76	10.0	0.004	69	0	NS	0.03
Energy/fatigue	93	3.3	NS	88	–5.0	0.004	0.002
Health distress	91	8.3	<0.001	88	1.4	NS	NS
Health transition	76	4.0	NS	78	1.4	NS	NS

[a]Scores at baseline and end of treatment ranged from 0 to 100, with higher scores and positive changes Indicating better health.
[b]Wilcoxon signed-rank test comparing the change from baseline to the end of the treatment within treatments.
[c]Wilcoxon rank-sum test comparing the change from baseline to end of treatment between treatments.
Abbreviations: ABV, doxorubicin, bleomycin, vincristine; NS, not significant.

There was a significant difference between the two treatments in four domains: general health, social functioning, and energy/fatigue. A clinically significant improvement was defined as a change of 10 points or more from baseline in the overall quality-of-life score, and more patients in the PLD group than the ABV group achieved this endpoint (65% vs 43%, p = 0.0008). The duration of clinically significant improvement in overall quality of life was also longer in the PLD-treated group than in the ABV group (p = 0.049).

To determine whether the addition of other agents to PLD might lead to improved treatment outcome, the AIDS Clinical Trials Group performed a study which randomized patients who had not received prior chemotherapy to receive treatment with PLD (20 mg/m^2) either alone or in combination with BV (bleomycin 10 U/m^2, and vincristine 1 mg), administered every 2 weeks (Misuyasu et al 1997). Among 126 evaluable patients, overall responses were similar in the two groups: 79% with PLD alone versus 80% when combined with BV. Five patients in each group experienced a CR. Median time to tumor progression or death was also similar: 29 and 32 weeks, respectively. Patients treated with PLD alone showed a trend toward better survival at the time of an interim analysis; with the single-agent, quality of life decreased less rapidly during treatment. The authors concluded that adding BV to PLD offered no additional benefit.

Safety of pegylated liposomal doxorubicin in clinical trials

Toxicities observed in phase I/II studies of PLD for KS are shown in Table 4 (Hengge et al 1993; Bogner et al 1994; Harrison et al 1995; Goebel et al 1996; Northfelt et al 1997; Grunaug et al 1998; Newell et al 1998). Neutropenia was progressive with succeeding courses of PLD and was the most common dose-limiting side effect, with an incidence that ranged from 28.6% to 85% in various trials. This wide variation was likely related to the degree to which AIDS had compromised the marrow in addition to the effects of prior chemotherapy. In these trials, the overall incidences of alopecia and nausea and vomiting were low (generally <20%). In contrast to studies of patients with solid tumors in which PLD was administered at a higher dose, the incidences of hand-foot syndrome (HFS; 0%–2%) and infusion reactions (0%–15%) were relatively low. Infusion reactions to PLD were characterized by some or all of the following: flushing, tachycardia, dyspnea, hypertension or hypotension, chest pain, abdominal pain, and back pain.

Table 4 Efficacy of pegylated-liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma after failure of standard chemotherapy: adverse events (Northfelt et al 1997)

Event (n = 53)	All events[a] (% patients)	Severe (% patients)
Any adverse event	76%	30%
Leukopenia	40%	17%
Nausea and/or vomiting	19%	0%
Alopecia	9%	0%
Asthenia	9%	2%
Fever	8%	2%
Diarrhea	6%	2%
Thrombocytopenia	6%	2%

[a]Adverse events occurring in ≥5% of patients, thought to be possibly or probably related to pegylated-liposomal doxorubicin.

A similar safety profile was observed in the phase III randomized comparisons of PLD and either BV or ABV (Stewart et al 1998; Northfelt et al 1998). Compared with these combination regimens, PLD was associated with a reduced incidence of nausea/vomiting, alopecia, and neuropathy (from vincristine, which is used in both the BV and ABV regimens) (Table 5). In the trial of PLD vs ABV (Northfelt et al 1998) myelosuppression and fever were less severe with PLD, but this did not translate into a reduced incidence of infection. In the comparison with BV (Stewart et al 1998), PLD was more myelosuppressive because neither bleomycin nor vincristine is associated with substantial bone marrow toxicity. HFS was uncommon with the PLD doses and schedules used in these trials. No cases occurred in either group of one trial (Stewart et al 1998), and in the other trial, 4% of PLD-treated patients and 1% of ABV-treated patients experienced HFS (Table 5). Mucositis, stomatitis, and infusion reactions such as dyspnea and hypotension occurred more frequently on the PLD arms; infusion reactions that occurred with BV consisted primarily of fever and rigors.

Comparative trial: PLD vs DNX

PLD was initially granted "accelerated approval" by the US FDA, when the only data available for regulatory review were from uncontrolled trials in patients with AIDS-KS which was refractory to conventional therapy, or in patients who were intolerant of conventional chemotherapy regimens. At the request of the US FDA, a double-blind randomized trial of PLD and DNX treatment for AIDS-KS was undertaken primarily to confirm earlier data for PLD, rather than as a comparison between the two drugs (Henry et al 2002). In this trial patients were randomized in a 3:1 ratio to receive PLD or DNX, respectively. The nature of the trial and the small number of patients enrolled precluded a robust statistical analysis, and p values were not calculated.

For enrollment patients were required to have at least one KS-related symptom at baseline so that clinical benefit could be assessed. Patients were initially eligible only if they were refractory to conventional chemotherapy, but the trial was ultimately amended to allow patients without or with limited prior chemotherapy because of slow accrual to the study. As a result, 7 of 80 patients enrolled had received prior chemotherapy. Patients were randomized to PLD 20 mg/m^2 or DNX 40 mg/m^2 given intravenously every 2 weeks for up to six cycles.

Although statistical tests were not performed, differences in clinical benefit and tumor response tended to favor PLD (n = 60) over DNX (n = 19) among the patients who received at least one dose of study treatment (Table 6). Clinical benefit was defined as improvement from baseline in at least one

Table 5 Incidences (%) of adverse events in randomized trials comparing a liposomal anthracycline with ABV or BV

	Stewart et al 1998			Northfelt et al 1998		
	PLD (Doxil) (n = 121)	BV (n = 120)	P value	PLD (Doxil) (n = 133)	ABV (n = 125)	P value
Neutropenia grade 3/4	72	51	<0.001	36	42	
Neutropenia grade 4	29	13		6	14	
G-CSF required				44	53	
Fever	16	25	0.08	0	5	
Sepsis	7	2		6	2	
OIs	50	30	<0.002	37	30	
Oral candidiasis	31	17	0.02			
Anemia	18	15		10	11	
Thrombocytopenia	15	12		3	6	
Alopecia	3	8		1	19	<0.001
Neuropathy – all grades	3	14	<0.005			
Neuropathy grade 3/4				6	14	0.002
Constipation	2	11	<0.01			
Nausea (all grades)	12	17				
Nausea/vomiting grade 3/4	16	25		15	34	<0.001
Stomatitis grade 3/4	7	5		5	2	0.026
Infusion reactions	4	6		5	0	
Skin rash	12	9				
Hand-foot syndrome[a]	0	0		4	1	

[a]Includes 2 skin rashes in PLD treated patients not called hand-foot syndrome but totally consistent with the syndrome.
Notes: Unless noted, differences are not statistically significant.
Abbreviations: ABV, doxorubicin, bleomycin, vincristine; BV, bleomycin, vincristine; G-CSF, granulocyte colony-stimulating factor; OI, opportunistic infection.

AIDS-KS symptom category that lasted for 28 days or longer in the absence of disease progression or severe drug-induced toxicity. Using this definition, 80% of PLD-treated patients and 63% of DNX-treated patients experienced clinical benefit. The definition of sustained clinical benefit was more restrictive, and involved improvement in at least one symptom category for 28 days or longer with no worsening of other symptom categories and no increase in medical interventions either before or during that period. Sustained clinical benefit was observed in 37% of PLD-treated patients and 16% of DNX-treated patients. An external HIV/AIDS expert who was blinded to treatment allocation determined that clinical study photographs showed clinical efficacy rates of 35% for PLD and 38% for DNX.

Partial tumor response was defined as one or more of the following: (1) no new lesions (skin or oral), no new visceral sites of involvement, no appearance or worsening of tumor-associated edema or effusions, and a 50% or greater decrease in the number of all previously existing lesions lasting for at least 4 weeks; (2) complete flattening of at least 50% of all previously raised lesions; (3) a 50% decrease in the sum of the products of the largest perpendicular diameters of the indicator lesions; or (4) the patient met the criteria for complete clinical response except residual tumor-associated edema or effusion. Using these criteria, 55% of patients in the PLD group and 32% of patients in the DNX group had a PR to liposomal anthracycline therapy. There was a positive correlation between clinical benefit and tumor response (Pearson correlation coefficient, 0.25; $p = 0.028$). Ninety-two percent of patients who responded to PLD experienced clinical benefit, and 42% of responders in the PLD group experienced sustained clinical benefit.

There were concerns that the introduction of HAART, which occurred around the time the study began to enroll patients, might have confounded the results of the study. An additional analysis of the data thus considered antiretroviral therapy to be a potential confounding factor if it was begun within 28 days of study entry or was changed during the study. The observed rates of clinical benefit were not significantly different between patients who met these criteria for potentially confounding treatment and those who did not (26% and 35%, respectively; $p = 0.461$).

Differences in the nature and frequency of side effects from the two drugs were smaller than might have been expected from indirect comparisons drawn from data shown in Tables 6 and 7. HFS and infusion reactions were seen only with PLD. In all but one of the patients who experienced HFS or infusion reactions, the reactions were grade 1/2, and none of the reactions caused patients to discontinue treatment.

Conclusion

Many new and interesting agents are under development for treating AIDS-KS, including angiogenesis inhibitors, locally applied and oral retinoids, more effective anti-retroviral agents, and drugs targeting HHV-8. However, liposomal anthracyclines are still considered by many to be the initial drugs of choice for this disease when it is advanced and symptomatic.

Phase 1 clinical trials confirmed that delivery via pegylated liposomes does concentrate doxorubicin in AIDS-KS lesions more effectively that does treatment with conventional doxorubicin, as well as concentrating doxorubicin to a greater degree in AIDS-KS lesions than in adjacent normal skin (Northfelt et al 1993, 1995). A number of phase II clinical trials demonstrated substantial effectiveness and good tolerability of PLD in treatment of AIDS-KS, even in patients who had previously been treated with conventional chemotherapy, including conventional doxorubicin (Sturzl et al 1994; Hengge et al 1993, 2001; Simpson et al 1993; Bogner et al 1994; James et al 1994; Wagner et al 1994; Bergin et al 1995; Harrison et al 1995; Goebel et al 1996; Northfelt et al 1997; Grunaug et al 1998; Newell et al 1998; Nuncez et al 2001).

Finally, in phase III clinical trials in which PLD compared with conventional treatment with BV or ABV, PLD was associated with a higher response rate, shorter time to response, and less toxicity in patients with AIDS-KS (Stewart et al 1998; Northfelt et al 1998). PLD also improved several domains of health-related quality of life compared with ABV (Osoba et al 2001). Thus, liposomal anthracyclines, and in particular PLD, appear to offer comparable or superior efficacy, improved tolerability, and improved quality of life relative to conventional chemotherapy for AIDS-KS, validating the theoretical advantage of pegylated liposomal drug delivery in this disease.

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