Doxorubicin (as pegylated liposomal)

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.1. Cytotoxic medicines

EMLc | ATC codes: L01DB01

Indication	Kaposi sarcoma of unspecified primary site ICD11 code: 2B57.Z
INN	Doxorubicin
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 2 mg per mL in 10 mL vial (hydrochloride) ; 2 mg per mL in 25 mL vial (hydrochloride)
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Doxorubicin (as pegylated liposomal)
DrugBank	Doxorubicin (as pegylated liposomal) (Doxorubicin)

Expert Committee recommendation

The Expert Committee acknowledged the public health relevance of effective treatments for Kaposi sarcoma, also noting that this disease disproportionately affects people in low- and middle-income countries. The Committee considered that the evidence presented from several clinical trials suggests that PLD is superior in efficacy to the alternative chemotherapy regimens involving bleomycin, vincristine or vinblastine, with or without non-liposomal doxorubicin or daunorubicin. It is also non-inferior to paclitaxel. In addition, PLD may be associated with reduced harms compared with alternative chemotherapies. The Committee considered the comments of the Cancer Medicines Working Group that reiterated the relevance of paclitaxel as first-line chemotherapy for Kaposi sarcoma, which is associated with similar clinical benefits as PLD in adults and may be more widely available and affordable. However, the Committee noted that paclitaxel is associated with higher toxicities than PLD, especially neutropenia and sensory neuropathy. Therefore, the Committee considered that the addition of PLD may offer an additional option with a more favourable side-effect profile and dosing schedule. The Committee also noted that PLD may be preferable to paclitaxel for children with Kaposi sarcoma, as experience with paclitaxel in this population is still limited. The Expert Committee therefore recommended the inclusion of PLD on the complementary list of the EML and EMLc for the treatment of Kaposi sarcoma.

Background

Currently included medicines for Kaposi sarcoma on the Model Lists include bleomycin, doxorubicin, paclitaxel (EML only), vinblastine and vincristine. Doxorubicin is included only in its non-pegylated liposomal form. During the comprehensive review of cancer medicines conducted in 2015, pegylated liposomal doxorubicin for Kaposi sarcoma was not proposed for consideration by the Expert Committee. At that time, the superiority of PLD over the doxorubicin + bleomycin + vincristine (or vinblastine) regimen had not been demonstrated, and its substantially higher cost did not justify its potential benefits in

resource-constrained settings (1). Since then, additional clinical evidence has been published and lower-cost sources for pegylated liposomal doxorubicin have become available.

Public health relevance

Kaposi sarcoma is a soft tissue cancer arising from lymphatic endothelial cells and caused by human herpesvirus 8. Different types exist: AIDS-related Kaposi sarcoma, iatrogenic Kaposi sarcoma and classical Kaposi sarcoma. More than 80% of Kaposi sarcoma occurs in low- and middle-income countries, with more than 60% occurring in the WHO African region. A disproportionately large proportion of deaths from Kaposi sarcoma (85%) occurs in Africa (2). In some areas with high HIV prevalence, Kaposi sarcoma is the most frequent type of cancer documented in registries (3). The incidence of paediatric Kaposi sarcoma is highly concentrated in Africa (95% of all cases globally), where it is the sixth most common cancer in young people aged 0–19 years, with more than 2000 new cases in 2020 (2).

Benefits

The application presented evidence of the clinical benefit of pegylated liposomal doxorubicin in Kaposi sarcoma from seven randomized and two observational studies, identified through a comprehensive literature search. A randomized, open-label, multicentre study compared PLD together with highly active antiretroviral therapy (HAART) versus HAART alone in 28 patients with HIV and moderate-advanced Kaposi sarcoma (4). At 48 weeks, 10/13 (77%) patients in the PLD+HAART group and 3/15 (20%) in the HAART alone group achieved complete or partial remission (risk ratio (RR) 3.80, 95% confidence interval (CI) 1.34 to 11.00; low-certainty evidence). A cohort study found no significant difference in overall survival at 12 months in patients with T1 (poor risk) Kaposi sarcoma treated with liposomal anthracyclines plus HAART versus HAART alone (5–7), however the study was not designed to compare treatment arms, nor was it powered to detect survival differences. A randomized, phase II study evaluated the efficacy and safety of liposomal doxorubicin alone or in combination with bleomycin plus vincristine in the treatment of AIDS-related Kaposi sarcoma (8). No significant differences were observed between treatment arms for overall response (RR 0.97, 95% CI 0.81 to 1.17; moderate-certainty evidence), complete response (RR 1.03, 95% CI 0.31 to 3.99; low-certainty evidence) or partial response (RR 0.96, 95% CI 0.77 to 1.21; moderate-certainty evidence). Two randomized studies compared PLD with bleomycin and vincristine in patients with AIDS-related Kaposi sarcoma (9,10). The first study found moderate- or high-certainty evidence of no significant difference in tumour response measures between treatment groups (9). The second study found that at the end of treatment, the PLD group had significantly higher rates of overall response (38.8% versus 14.2%; RR 2.74, 95% CI 1.67 to 4.49; high-certainty evidence) and other response measures compared to bleomycin with vincristine (10). A randomized, phase III clinical trial evaluated PLD versus doxorubicin + bleomycin + vincristine in 258 adults with AIDS-related Kaposi sarcoma (11). A partial response to treatment was achieved by 60/133 (45.1%) of patients in the PLD group versus 31/125 (24.8%) in the doxorubicin + bleomycin + vincristine group (RR 1.82, 95% CI 1.27 to 2.60; high-certainty evidence). No significant difference was found in overall survival between treatment groups (RR for death 1.41, 95% CI 0.79 to 2.53; high-certainty evidence), with median survival duration of about 160 days in each group. An observational study evaluated survival in 29 patients with pulmonary Kaposi sarcoma. Patients received liposomal doxorubicin, bleomycin and vinblastine or vincristine, or no chemotherapy (12). Mean survival time for patients who received liposomal doxorubicin was significantly higher (11.8 months versus 4.4 months). A randomized trial compared the efficacy and toxicity of PLD and paclitaxel in 73 patients with AIDS-related Kaposi sarcoma, with 73% of participants receiving HAART (13). No significant differences between treatment groups were observed for overall survival, progression-free survival or tumour response. A prospective, single-arm, observational study in Mozambique in 116 patients with AIDS-associated Kaposi sarcoma, found that PLD had an overall response rate of 80% (14). The authors noted that response with PLD was achieved faster than had been observed with doxorubicin + bleomycin + vincristine in the same treatment centres in an earlier study (eight or fewer cycles with PLD versus 12 cycles with doxorubicin + bleomycin + vincristine).

Harms

The randomized trial comparing PLD with the doxorubicin + bleomycin + vincristine regimen (11) reported that PLD had significantly lower rates of: grade 3 and 4 peripheral neuropathy (6% (8/133) versus 14% (17/125), $P = 0.002$)); nausea or vomiting (15% (20/133) versus 34% (42/125), $P < 0.001$)); and alopecia (1% (1/133) versus 19% (24/125), $P < 0.001$)). The rate of mucositis/stomatitis was significantly higher in patients receiving PLD (5% (6/133) versus 2% (2/125), $P = 0.026$). No significant differences were found between treatment groups in overall grade 3 and 4 adverse events, grade 3 and 4 anaemia or grade 3 and 4 leukopenia. When interpreting these findings, it is important to note that these patients did not receive HAART, and all patients died by 6 months of follow-up. Median CD4 count was 13.0 cells/microlitre in the doxorubicin + bleomycin + vincristine group and 12.5 cells/microlitre in the PLD group. The randomized trial comparing PLD with bleomycin + vincristine (10) reported that PLD had a significantly lower rate of paraesthesia (3.3% versus 14.2%, $P < 0.005$) and

constipation (1.7% versus 10.8%, P < 0.01), a higher rate of leukopenia (71.9% versus 50.8%, P < 0.001) and opportunistic infections (49.6% versus 30.0%, P < 0.002). No significant differences were found between treatment groups in the overall rate of adverse events of any severity. When interpreting these findings, it is important to note that these patients did not receive HAART, although 48.8% of patients in the PLD arm and 56.7% in the bleomycin + vincristine arm were taking one or more antiretroviral drug. The randomized trial comparing PLD with paclitaxel (13) reported a higher incidence of grade 3 or higher toxicity in the paclitaxel arm, although the difference was not significant (84% versus 66%, P = 0.077). Similarly, grade 3 and 4 neutropenia occurred more frequently in the paclitaxel group (58% versus 41%, P = 0.184). The incidence of grade 1 and 2 alopecia was significantly higher in the paclitaxel arm (58% versus 11%, P < 0.001) as was the incidence of sensory neuropathy (26% versus 9%, P = 0.045). This trial (with 82 patients included in the toxicity comparison) was not powered to detect a clinically significant difference in neutropenia rates. A 2020 meta-analysis of PLD versus paclitaxel as first-line treatment for ovarian cancer (any stage) found that paclitaxel was associated with significantly higher rates of neurotoxicity (RR 5.59, 95% CI 1.43 to 21.84) and allergy (RR 1.8, 95% CI 1.06 to 3.24), and higher rates of leukopenia (RR 1.55, 95% CI 0.99 to 2.44) (15). No significant differences were found in rates of neutropenia (RR 1.03, 95% CI 0.78 to 1.35), cardiotoxicity (RR 0.51, 95% CI 0.06 to 3.99), fatigue (RR 0.84, 95% CI 0.53 to 1.34) or nausea/vomiting (RR 0.66, 95% CI 0.32 to 1.37). Adverse events that were significantly more common with PLD included anaemia and thrombocytopenia (15). A 2021 meta-analysis of PLD versus paclitaxel in recurrent ovarian cancer found that, compared with paclitaxel plus carboplatin, PLD plus carboplatin had significantly lower rates of neutropenia, allergic reactions and arthralgia/myalgia. Anaemia and thrombocytopenia were significantly more common in the PLD arm than the paclitaxel arm (16). The most commonly reported adverse events with PLD in the product information documents of the United States Food and Drug Administration and the European Medicines Agency were haematological (thrombocytopenia, anaemia and neutropenia). The most common non-haematological adverse event reported was nausea (17,18). The medicine carries a box warning in the United States for infusion reactions, myelosuppression, cardiotoxicity, liver impairment and substitution with non-liposomal doxorubicin (17).

Cost / cost effectiveness

The application identified six studies that evaluated the cost–effectiveness of PLD versus various comparators including: liposomal daunorubicin; bleomycin + vincristine; doxorubicin + bleomycin + vincristine; paclitaxel; and oral etoposide (20–25). In general, these studies suggest that PLD is a cost-effective treatment compared with liposomal daunorubicin but less cost-effective when compared with bleomycin + vincristine or doxorubicin + bleomycin + vincristine or paclitaxel. The application also presented a comparison of the price per treatment cycle of PLD and paclitaxel in selected countries which showed substantial variation across settings. For example, prices per treatment cycle for PLD ranged from about US$ 150 in India to US$ 709 in Brazil. Prices per treatment cycle for paclitaxel were lower, ranging from US$ 42 in Indonesia and Ukraine to US$ 350 in Brazil and El Salvador.

WHO guidelines

The 2014 WHO guidelines on the treatment of skin and oral HIV-associated conditions in children and adults recommend immediate initiation of antiretroviral therapy in adults, adolescents and children living with HIV who are diagnosed with mild-to-moderate Kaposi sarcoma and immediate initiation of antiretroviral therapy in combination with systemic chemotherapy in adults, adolescents and children living with HIV who are diagnosed with severe symptomatic Kaposi sarcoma. Recommended chemotherapy regimens in adults, adolescents and children may include: doxorubicin + bleomycin + vincristine; bleomycin + vincristine; and, when available or feasible, liposomal anthracyclines (doxorubicin or daunorubicin), paclitaxel or oral etoposide at sites with the infrastructure, staff and resources to administer chemotherapy drugs and provide appropriate monitoring and supportive care (19).

Availability

PLD has regulatory approval globally for several indications, including Kaposi sarcoma. It is available in innovator and generic brands. PLD is also available for pooled procurement from the Global Fund, as a strategic medicine used in HIV programmes.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department commented that while some data supported the clinical value of PLD with reduced toxicity (including cardiotoxicity) compared with non-pegylated doxorubicin, mature overall survival data were insufficient to fully evaluate its candidacy for inclusion on the Model Lists, particularly given that alternative, established regimens were already included. The EML Cancer Medicines Working Group reviewed the application and advised that it supported the inclusion of pegylated liposomal doxorubicin on the Model Lists for the treatment of advanced-stage Kaposi sarcoma in adults

and children based on a positive benefit–risk profile. The Working Group noted that PLD was associated with relevant survival benefits for patients and reduced harms when compared with other chemotherapies (bleomycin, vinblastine, vincristine, vinorelbine and etoposide). The Working Group reiterated the relevance of paclitaxel for Kaposi sarcoma, as it is associated with benefits similar to PLD in adults and it is likely to be more available than PLD in resource-constrained settings. However, paclitaxel is associated with higher toxicity compared with PLD, particularly neutropenia and sensory neuropathy. While generics of PLD are becoming more available, the Model List must reiterate the relevance of paclitaxel as first-line chemotherapy for adult patients with advanced AIDS-associated Kaposi sarcoma in sub-Saharan Africa.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994; https://apps.who.int/iris/handle/10665/189763, accessed 6 October 2023).
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. Lyon: International Agency for Research on Cancer; 2020 (https://gco.iarc.fr/today, accessed 6 October 2023).
3. Carrilho C, Ferro J, Lorenzoni C, Sultane T, Silva-Matos C, Lunet N. A contribution for a more accurate estimation of the incidence of Kaposi sarcoma in Mozambique. Int J Cancer. 2013;132(4):988–9.
4. Martin-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS. 2004;18(12):1737–40.
5. Bower M, Weir J, Francis N, Newsom-Davis T, Powles S, Crook T, et al. The effect of HAART in 254 consecutive patients with AIDS-related Kaposi's sarcoma. AIDS. 2009;23(13):1701–6.
6. Letang E, Lewis JJ, Bower M, Mosam A, Borok M, Campbell TB, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS. 2013;27(10):1603–13.
7. Bower M, Dalla Pria A, Coyle C, Andrews E, Tittle V, Dhoot S, et al. Prospective stage-stratified approach to AIDS-related Kaposi's sarcoma. J Clin Oncol. 2014;32(5):409–14.
8. Mitsuyasu R, von Roenn J, Krown R. Comparison study of liposomal doxorubicin (DOX) alone or with bleomycin and vincristine (DBV) for treatment of advanced AIDS-associated Kaposi's sarcoma (AIDS-KS): AIDS clinical trial group (ACTG) protocol 286. Proc Annu Meet Am Soc Clin Oncol. 1997;16:A191.
9. Rizzardini G, Pastecchia P, Vigevani GM. Stealth liposomal doxorubicin or bleomycin/vincristine for the treatment of AIDS related Kaposi's sarcoma. JAIDS. 1997;14(4):A20.
10. Stewart S, Jablonowski H, Goebel FD, Arasteh K, Spittle M, Rios A, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol. 1998;16(2):683–91.
11. Northfelt DW, Dezube BJ, Thommes JA, Miller BJ, Fischl MA, Friedman-Kien A, et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol. 1998;16(7):2445–51.
12. Grünaug M, Bogner JR, Loch O, Goebel FD. Liposomal doxorubicin in pulmonary Kaposi's sarcoma: improved survival as compared to patients without liposomal doxorubicin. Eur J Med Res. 1998;3(1–2):13–9.
13. Cianfrocca M, Lee S, Von Roenn J, Tulpule A, Dezube BJ, Aboulafia DM, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer. 2010;116(16):3969–77.
14. Coldiron ME, Gutierrez Zamudio AG, Manuel R, Luciano G, Rusch B, Ciglenecki I, et al. Outcomes of AIDS-associated Kaposi sarcoma in Mozambique after treatment with pegylated liposomal doxorubicin. Infect Agent Cancer. 2021;16(1):2.
15. Shi SQ, Jiang FF, Hong T, Zhuang Y, Chen L, Huang XL. Comparison of pegylated liposomal doxorubicin and paclitaxel plus carboplatin-based chemotherapy as first line treatment for patients with ovarian cancer: a systematic review and meta-analysis of randomized controlled trials. Eur Rev Med Pharmacol Sci. 2020;24(6):2911–27.
16. Li X-R, Zhu Y, Zhang G-N, Huang J-M, Pei L-X. The impact of pegylated liposomal doxorubicin in recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials. J Ovarian Res. 2021;14(1):42.
17. Prescribing information. DOXIL (doxorubicin hydrochloride liposome injection) for intravenous infusion. Bethesda, MD: U.S. Food and Drug Administration; 2007 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf, accessed 6 October 2023).
18. Summary of product characteristics – Caelyx (pegylated liposomal doxorubicin hydrochloride). Amsterdam: European Medicines Agency; 2023 (https://www.ema.europa.eu/en/documents/product-information/caelyx-pegylated-liposomal-epar-product-information_en.pdf, accessed 6 October 2023).
19. Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/136863, accessed 6 October 2023).
20. Bennett CL, Golub RM, Stinson TJ, Aboulafia DM, von Roenn J, Bogner J, et al. Cost-effectiveness analysis comparing liposomal anthracyclines in the treatment of AIDS-related Kaposi's sarcoma. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18(5):460–5.
21. Hjortsberg C, Persson U, Lidbrink E, Bennett C. Cost-effectiveness analysis of pegylated-liposomal doxorubicin and liposomal daunorubicin treatments in patients with Kaposi's sarcoma. Acta Oncol. 1999;38(8):1063–7.
22. Bennett CL, Calhoun EA. Pharmacoeconomics of liposomal anthracycline therapy. Semin Oncol. 2004;31:191–5.
23. Vanni T, Fonseca BAL, Polanczyk CA. Cost-effectiveness analysis comparing chemotherapy regimens in the treatment of AIDS-related Kaposi's sarcoma in Brazil. HIV Clin Trials. 2006;7(4):194–202.
24. Raimundo K, Biskupiak J, Goodman M, Silverstein S, Asche C. Cost effectiveness of liposomal doxorubicin vs. paclitaxel for the treatment of advanced AIDS–Kaposi's sarcoma. J Med Econ. 2013;16(5):606–13.
25. Freeman EE, McCann NC, Semeere A, Reddy KP, Laker-Oketta M, Byakwaga H, et al. Evaluation of four chemotherapy regimens for treatment of advanced AIDS-associated Kaposi sarcoma in Kenya: a cost-effectiveness analysis. Lancet Glob Health. 2022;10(8):e1179–e88.