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Efficacy of paclitaxel in the treatment of Kaposi sarcoma

V. ERCOLAK, B. SAHIN, M. GUNALDI, B.B. DUMAN, C.U. AFSAR

Department of Medical Oncology, Cukurova University Medical Faculty, Adana, Turkey

Abstract. – OBJECTIVE: Kaposi sarcoma is an angioproliferative disease. Kaposi sarcoma is clinicopathologically classified into four subgroups based on epidemiological data. For its systemic treatment, in addition to some chemotherapeutics, taxanes have also been used during the recent years for their anti-angiogenic properties. In this study, we aimed to compare paclitaxel and non-paclitaxel chemotherapeutic regimens in terms of efficacy and side effects.

PATIENTS AND METHODS: In our center, demographical, clinical and histopathological characteristics of a total of 13 patients diagnosed with Kaposi sarcoma who received therapy were retrospectively recorded based on their medical files.

RESULTS: Among these subjects, 7 have been treated with paclitaxel and 6 with non-paclitaxel therapies. Eleven patients were male. Twelve patients were found to have classical type of Kaposi Sarcoma. The recurrence was observed in 2 patients treated with paclitaxel and in 1 patient treated with non-paclitaxel therapy. No statistically significant difference was found between the therapeutic modality, the stage of the disease and the percentage of the recurrence. Neuropathy developed in 3 patients treated with paclitaxel, whereas there was no neuropathy in the other group. Although the recurrence-free survival was worse in the patients treated with paclitaxel, there was no statistically significant difference.

CONCLUSIONS: Cytotoxic chemotherapy is effective in treating patients with Kaposi Sarcoma, although it is palliative. Taxanes have demonstrated effectiveness against AIDS-associated Kaposi Sarcoma. The experience suggests that paclitaxel is an effective alternative in the treatment of classical form Kaposi's sarcoma. There was no difference in efficacy between paclitaxel and non-paclitaxel therapies whereas difference in occurrence of neuropathy which is one of the side effects, showed borderline statistical significance.

Key Words:

Kaposi sarcoma, Neuropathy, Non-paclitaxel therapies, Paclitaxel, Taxane.

Introduction

Kaposi sarcoma is an angioproliferative disease characterized by the proliferation of the endothelial cell-derived predominant fusiform cells, neoangiogenesis, inflammatory cell infiltration and edema[1]. Kaposi sarcoma is clinicopathologically classified into four subgroups based on epidemiological data. Classical Kaposi sarcoma is the first described type of the silent cutaneous proliferative disease that primarily affects elderly men with Mediterranean and Jewish ethnicity. It is a type with good prognosis, which commonly involves the skin of the distal lower extremity with visceral organ involvement in some cases. Endemic or African type is the type with the poorest prognosis that is seen in all parts of the Equatorial Africa, and consists of several subtypes and is more commonly seen in men. The type observed in the organ transplant receivers is known as a type that is probably related to immunosuppression, is equally seen among the two genders, may regress after the discontinuation of the therapy and may show an aggressive and multifocal course compared to classical type. The last type is the type seen in HIV-infected individuals. It is the most common malignancy in the cases of AIDS. It is a type which is seen at an earlier age compared to classical type, which may be multifocal and which may involve visceral organs along with mucosal surfaces. In all types of Kaposi sarcoma, Kaposi sarcoma-related human herpes virus, which is a gamma herpes virus, was detected and its importance in the development of Kaposi sarcoma has been better understood today[2].

Although its incidence varies across different types, most common presentation is purple, blue-red or dark brown, black macula, papule, plaque and nodular skin lesions and accompanying lymphedema, especially in the lower extremities[3]. Unlike AIDS-related Kaposi sarcoma, classical

Corresponding Author: Vehbi Ercolak, MD; e-mail: vehbiercolak@hotmail.com

Kaposi sarcoma does not have a widely used and internationally accepted staging system. Usually it is divided into four stages according to a staging system which was developed based on progression rate and dissemination of the disease observed in 300 patients with classical Kaposi sarcoma by Brambilla et al[4]. Stage 1 is the maculonodular stage which consists of small maculas and nodules in the lower extremity, stage 2 is the infiltrative stage that consists of mainly plaque and occasionally related to small nodules in the lower extremities, stage 3 is the florid stage characterized by ulcerated multiple angiomatous plaques and nodules, and stage 4 is the disseminated stage where multiple angiomatous nodules and plaques are localized in the lower extremity. While all Stage 1-3 patients are considered to be either slowly progressing (1) or rapidly progressing (2), all stage 4 patients are considered as rapidly progressing. Based on this classification, stage 1-2 patients show slower progression, less complications and less gastrointestinal and visceral involvement, whereas stage 3-4 patients express features that are contrary to these findings[4].

As treatment, local and systemic therapies are given to these patients in order to reduce the tumor size, to decrease the symptom severity and to prevent the disease progression. For the patients with limited number of asymptomatic lesions and functional impairment only monitoring is considered, whereas for the patients with the symptoms caused by limited volume of disease or cosmetic problems local therapies (RT, excision, cryo, laser ablation) should be considered. Despite the lack of a consensus for defining this condition as a systemic disease, systemic therapy may be considered in the patients with symptomatic visceral and mucosal involvement, diffuse symptomatic lesions in multiple parts of the body, a lesion which exceeds a single field of radiation, with extensive nodular disease or nodular disease that diffusely involve a large part of an extremity or moderate lymphedema that cannot be controlled with support bandage. For systemic therapy, in addition to the drugs such as anthracyclines, vinca alkaloids, bleomycin, oral etoposide and gemcitabine, taxanes have also been used during the recent years for their antiangiogenic effects[5]. Although the best and most efficient therapy for classical Kaposi sarcoma is controversial, currently most recommended therapy is doxorubicin which is a liposomal chemotherapeutic agent. In this study, we aimed to compare the efficacy and the side effects of paclitaxel and non-paclitaxel chemotherapy regimens used for the treatment because of the differences in national and regional reimbursement conditions of the chemotherapeutic drugs.

Patients and Methods

Demographical, clinical and histopathological characteristics of a total of 13 patients who were presented to our clinic, diagnosed with Kaposi sarcoma and received therapy between 2002 and 2011 were retrospectively recorded based on their medical files. All patients were HIV-negative and while one patient had transplantation-related Kaposi sarcoma, others had classical Kaposi sarcoma. Patient characteristics such as age, gender, tumor localization, type of Kaposi sarcoma, recurrence site, follow-up time, the therapy administered and the development of neuropathy were recorded. Staging was based on the staging system of Brambilla et al[4] and the patients were divided into two groups as stage 1-2 and stage 3-4 according to their physical examination and imaging results in their medical files. All but three patients were reached via telephone. The patients were divided into paclitaxel users and non-paclitaxel therapy users (mostly anthracycline-based, one radiotherapy).

Statistical Analysis

Between these two groups, survival analysis was performed using Kaplan-Meier analysis and binary analysis was performed using Chi-Square test. $p < 0.05$ was considered as statistically significant.

Results

Our patients were not eligible for local therapy because they either had lesions in more than one extremity or multiple lesions. Of these 13 subjects, 7 (53.8%) had been treated with paclitaxel and 6 (46.2%) with non-paclitaxel therapies. Eleven of the patients (84.6%) were men and 2 (15.4%) were women. Both women were treated with paclitaxel therapy and, of the remaining 11 patients, 5 were treated with paclitaxel and 6 with non-paclitaxel therapies. When the localizations of the lesions were considered, 6 patients had lesions localized only in the lower extremities (46.2%), 1 (7.7%) had lesions localized in the upper extremity and 6 (46.2%) had lesions

with multiple localizations. Of the patients, 7 (53.8%) were classified as stage 1-2 and 6 (46.2%) as stage 3-4 (Figure 1). While only one patient had post-transplantation Kaposi sarcoma, other 12 patients (92.3%) had classical Kaposi sarcoma. All cases were respondent to taxanes and non-taxanes treated. Three of the patients who were followed-up, 2 were treated with paclitaxel and 1 with non-paclitaxel therapy, had recurrence after the treatment. Recurrence site was lower extremity in two patients and upper extremity in 1 patient. Recurrence percentage was 28.6% in the patients treated with paclitaxel and 16.7% in those treated with non-paclitaxel therapies. When the time to recurrence was considered, mean time to recurrence was 15.5 months after the therapy completion in 2 patients and 12 months after the therapy completion in the users of non-paclitaxel therapy. No statistically significant difference was found between the therapeutic modality and the stage and the recurrence percentage (p = 0.391-0.612, respectively, using Pearson's Chi-Square).

Mean age of the patients treated with paclitaxel therapy was 63.86 years (median/min-max = 68/40-75) and 64.17 years (median/min-max = 53.5/51-75) in those treated with non-paclitaxel therapy (Table I). Although the patients treated with paclitaxel were claimed to be slightly younger, no statistical significance was found (p = 0,836) with regard to age of the patients. Mean follow-up time was 27,29 months (median/min-max = 24/2-75 months) in the patients treated with paclitaxel and 37,17 months (median/min-max = 28.5/5-71 months) in those treated with non-paclitaxel therapies, but no statistically significant difference was found between these two groups (p = 0.534). Mean duration of the therapy was 45.43 weeks in those treated with paclitaxel (median/min-max = 26/2-120 weeks). Neuropathy developed in 3 patients treated with paclitaxel (42.9%), whereas it did not develop in the patients treated with non-paclitaxel therapies. The occurrence of neuropathy was markedly higher in the group treated with paclitaxel. It was significant but it was a statistically borderline significance (p = 0.067). All but three patients were reached. Two patients died, one was being treated with paclitaxel and other with non-paclitaxel therapy. Despite the small number of patients, recurrence-free survival rate was found to be lower in the patients treated with paclitaxel but no statistically significant difference was found (p = 0.405) (Figure 2).

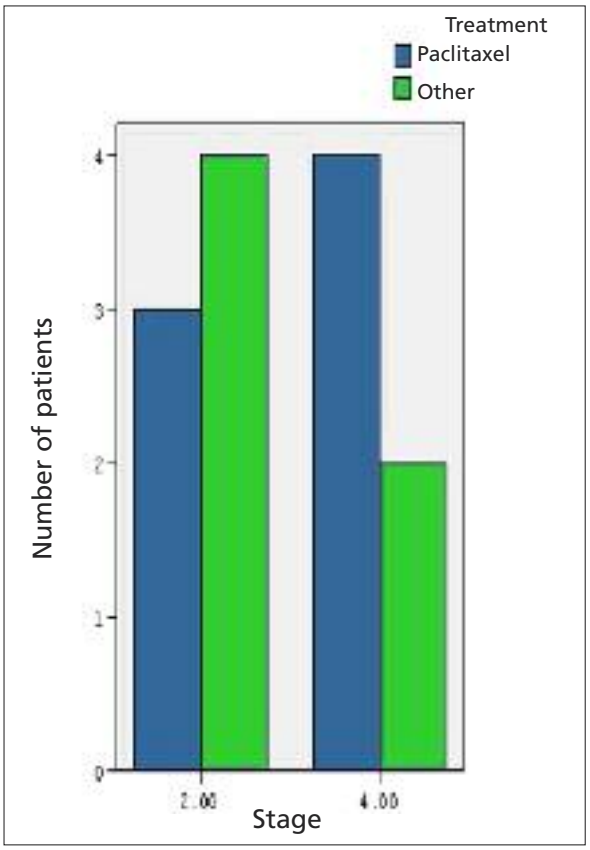

Figure 1. Therapeutic modality by stage.

Discussion

Cytotoxic chemotherapy is effective in treating patients with Kaposi sarcoma, although it is

Table I. Follow-up time, patient age, duration of paclitaxel therapies.

	Paclitaxel [x ± SD med (min; max)]		Non-Paclitaxel [x ± SD med (min; max)]		p
Follow-up time (months)	27.3 ± 26.5	24 (2; 75)	37.2 ± 25.8	28.5 (5; 71)	0.534
Patient age (year)	63.86 ± 4.39	68 (40-75)	64.17 ± 3.87	53.5 (51-75)	0.836
Pac. time (weeks)	45.43 ± 16.82	26 (2-120)	–	–	

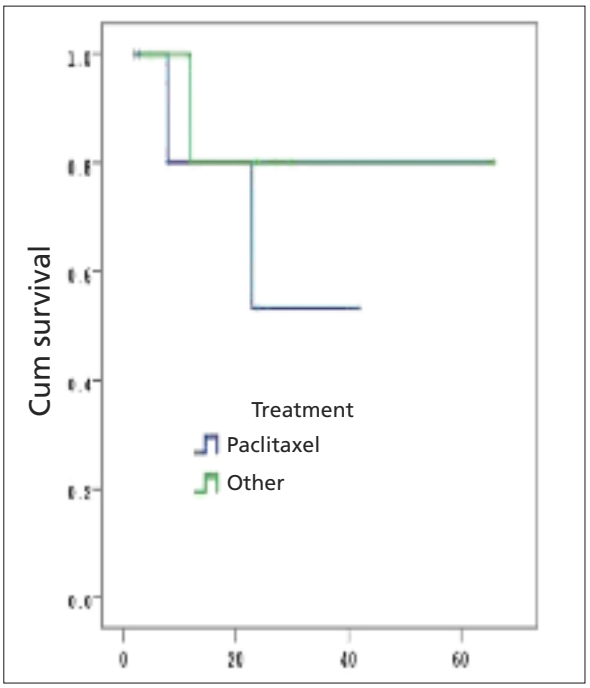

Figure 2. Recurrence-free survival curve.

palliative[6-13]. It is known that, in AIDS-related and classical Kaposi sarcoma, Bcl-2, a well-known proto-oncogene that antagonizes the apoptosis and that ensures prolonged cellular viability in the vessels and in the fusiform cells, is highly expressed[1]. Paclitaxel and docetaxel have potent antiangiogenic activities, which may explain their efficacy on Kaposi lesions[14,15]. Paclitaxel is both an agent that stabilizes the microtubules with its well-known action and an inhibitor of the antiapoptotic effect of Bcl-2[1].

Therapeutic options for Kaposi sarcoma are based upon disease stage, progression pattern and distribution, clinical type, and immune status[16,17]. For Kaposi sarcoma patients with more widely disseminated, progressive or symptomatic disease, systemic therapy with cytotoxic chemotherapy is generally warranted[18]. The treatment options for endemic and classic Kaposi sarcoma, when systemic treatment is required, are interferon, cytotoxic agents (vincristine, vinblastine, bleomycin, and etoposide) and anthracyclines also have been evaluated poorly, and their cardiotoxicity is a limiting factor for their use in elderly patients[19]. Taxanes have demonstrated effectiveness against AIDS-associated Kaposi sarcoma[13,20-24].

In fact, it is highly expressed in the literature and well-known that paclitaxel has a high efficacy as second-line therapy following anthracycline in the treatment of AIDS-related Kaposi sarcoma[20]. Recently, some articles about its efficacy in the treatment of classical, endemic and post-transplantation types of Kaposi sarcoma are also published[1,19,25-31]. In a study published in 2010[21], which compared paclitaxel and liposomal doxorubicin in 73 patients, while response rates (56%-46%), median PFS (17.5 months-12.2 months) and 2-year survival rates (79%-78%) favored paclitaxel, even if not significant, only toxicity (84%-66%) results did not favor paclitaxel. In one of the studies[30] 17 patients with classical Kaposi sarcoma were treated with paclitaxel, mean number of cycles given to the patients was 16.8 and the time to recurrence was 4.5 months after the treatment discontinuation and 7.35 months after the 12th cycle. In published studies[22-24], complete or partial response was achieved in 56-71.4% of AIDS-related patients with KS. In a large published study[22] (107 patients), the median duration of complete or partial response was 8.9 months and the median time to disease progression in responding patients was 12.9 months. In our study, recurrence percentage was 28.6% in the patients treated with paclitaxel, in a large published study (107 patients) was 21%[22].

In our study, paclitaxel was given for a mean period of 45 weeks (approximately 22 cycles) and the time to recurrence was found to be 15.5 months after the treatment discontinuation in the patients treated with paclitaxel. In published studies[19,22,24], the time to recurrence was found to be 8.9-13 months. Paclitaxel was given for a mean period of 20-21 weeks[19,24].

All but one of our patients had classical Kaposi sarcoma, which is most commonly seen between 40- and 70-years-of age. Consistent with the literature, majority of our subjects were male (84.6%) and mean age was 64 years[3,19,22].

In our patients majority of which were candidates for systemic therapy, the use of paclitaxel resulted in poorer survival, follow-up time and recurrence rates compared to other therapies but no statistical significance was found. This may be explained by the fact that the patients with advanced stage rather preferred paclitaxel.

In the literature, in a study[22] in which 107 patients were treated with paclitaxel the occurrence of peripheral neuropathy was found to be 47%, which was similar to the result found in our study (42.9%). In the group treated with non-paclitaxel therapy, the absence of neuropathy shows that neuropathy is the most important lim-

itation of this therapy. Furthermore, in this patient group with a mean age above 60-years, paclitaxel can be a good choice instead of anthracycline- and bleomycin-based therapies because the use of anthracycline is limited by cardiotoxicity and also these therapies cannot be frequently repeated like paclitaxel.

Conclusions

Paclitaxel has recently been shown to be effective in treating acquired immunodeficiency syndrome-associated Kaposi's sarcoma. The experience suggests that paclitaxel is an effective alternative in the treatment of classical form Kaposi's sarcoma. While there was no difference in efficacy between paclitaxel and non-paclitaxel therapies, difference in the occurrence of neuropathy that is one of the side effects, showed borderline statistical significance. Although paclitaxel seems to be efficient in this group of patients, it should be used with caution because it increases the risk for neuropathy.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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