American Journal of Transplantation 2002; 2: 877–879
Blackwell Munksgaard

ISSN 1600-6135

Case Report

Successful Treatment of Post-Renal Transplant Kaposi's Sarcoma with Paclitaxel

Nilesh Patel[a], Moro Salifu[b], Nablil Sumrani[c], Dale Distant[c], Joon Hong[c], Mariana Markell[b] and Albert S. Braverman[a],*

Divisions of [a]Hematology/Oncology and [b]Nephrology, Department of Medicine, and [c]Transplantation Division, Department of Surgery, Downstate Medical Center, State University of New York, Brooklyn, NY, USA
**Corresponding author: Albert S. Braveman, abraverman@netmail.hscbklyn.edu*

Kaposi's sarcoma (KS) is a complication of immunosuppressive therapy for renal transplant recipients. Treatment is usually withdrawal of immunosuppression; nonresponders often receive chemotherapy. Successful treatment with single agent paclitaxel (PTX) has been documented in only one patient. We report two patients with generalized cutaneous, and visceral KS, which progressed despite withdrawal of immunosuppressive therapy, and were treated with weekly PTX. Both patients' KS regressed completely after four courses of PTX, and remained in remission for >1 year. PTX may be important in the treatment of post-transplant KS resistant to withdrawal of immunosuppressive therapy.

Key words: Chemotherapy, Kaposi, paclitaxel, transplant

Received 14 January 2002, revised and accepted for publication 9 April 2002

Introduction

Kaposi's sarcoma (KS) accounts for 3–4% of the malignancies associated with immunosuppression for renal transplantation in the USA (1). Its prevalence in transplant recipients varies geographically, ranging from 0.17% in Africa and 0.06% in Germany, to 3.3% in Israel and 4.1% in Saudi Arabia (2). KS is also a common neoplasm of adult immunodeficiency syndrome (AIDS) patients. Both sporadic and opportunistic forms of KS are associated with the presence of the human herpes virus 8 (HHV8) genome in the neoplastic cells (3). Geographic variations in the incidence of KS in immunosuppressed patients may be due to differences in the frequency of subclinical HHV8 infection among these populations (4).

KS in renal transplant patients may present as localized cutaneous nodules, often on the legs, as in the sporadic form of the disease, or may involve the whole skin, and/or viscera. About 50% of cutaneous KS patients respond to withdrawal of immunosuppressive therapy (5). For those with persistent disseminated disease, various chemotherapeutic agents, and interferon, alone or in combination, have been used in small numbers of patients. We report complete remissions in response to weekly paclitaxel (PTX) in two patients with disseminated cutaneous, and visceral disease.

Methods and Patients

PTX disrupts normal microtubular protein function, thus acting as a mitotic inhibitor. Like vinblastine and vincristine, whose action mechanism is similar, PTX may cause peripheral neuropathy, a cumulative dose effect. Intravenous (i.v.) infusion of 60–100 mg/M^2 weekly, in 250 mL of normal saline solution over 1 h is as, or more effective than any other regimen, and minimizes and delays peripheral neuropathy (6,7). Responders, who have received 8 weekly treatments, are then crossed to treatment with the same dose every second week (8,9). Because of this drug's marked allergenicity, all patients are premedicated, either with the oral administration of 20 mg of dexamethasone 12 and 6 h prior to treatment, or by the infusion of 40 mg of dexamethasone i.v., 30 min prior to infusion. Immediately prior to infusion they also receive 50 mg of diphenhydramine and 300 mg of cimetidine i.v. Steroid dosages in responding patients without allergic reactions may be reduced to a minimum of 2.0 mg dexamethasone, in order to avoid steroid side-effects. Nausea does not occur, but alopecia is universal and granulocytopenia is common, though usually not severe. Sepsis did not occur in our patients, and therapy with granulocyte-colony stimulating factor (G-CSF) was not necessary. Myalgias may occur after the first few courses of treatment. Patients receiving PTX should be questioned about peripheral paresthesias before each course. Therapy must be discontinued if proprioceptive problems, such as inability to button clothes or write, develop, but, despite their prolonged treatment, our patients did not experience these complications.

Case 1

A 43-year-old African-American woman, with end-stage renal disease attributed to hypertension, received her first kidney transplant from an HLA identical 24-year-old brother, which failed after 8 years. After hemodialysis for 2 years she received a second living related kidney transplant from a 35-year-old brother. Normal graft function (serum creatinine 0.9–1 mg/dL) was maintained for 2 years with tacrolimus and prednisone. She then developed intractable spiking fevers, severe anemia, and edema. Bone marrow biopsy showed only hypocellularity and serous atrophy. There were no cu-

taneous lesions or adenopathy, and abdominal computer-automated tomography was negative. Because of her fevers, increasing asthenia, and a small amount of ascites, an exploratory laparotomy was performed, revealing diffuse infiltration of the peritoneum, and liver by KS. Tacrolimus was discontinued and steroid dose reduced to 5 mg/day, but her symptoms persisted. Although her extensive visceral malignancy might have ultimately regressed after withdrawal of immunosuppressive therapy, we did not feel justified in delaying treatment because of her persistent fevers, edema, anemia and moribund condition. Therefore, 2 weeks after termination of tacromolis, weekly PTX at 60 mg/m^2 was initiated, which resulted in almost immediate remission of her fevers, and rise in her hemoglobin from 7.5 to 9.5 g/dL. Her edema subsided, and she was able to return to work with a new baseline serum creatinine of 2.0 mg/dL. Four months later positron-emission tomography (PET) of her abdomen was negative. Five months after withdrawal of tacrolimus there was evidence of graft rejection, which was aborted by resumption of tacrolimus at a lower dose 1.0 mg twice daily. She remained on biweekly PTX for 12 months without significant toxicity, and remains in clinical remission after 15 months. Serum creatinine progressively increased to 7.6 mg/dL, requiring resumption of hemodialysis. The syndrome of anemia and fever with which she presented has been reported in HHV8 viremia (10). HHV8 studies performed 4 months after recovery were positive for antibody, but PCR was negative for HHV8 antigen.

Case 2

After 6 years on cyclosporine and prednisone for a cadavaric renal transplant, a 74-year-old ethnic Albanian woman from Montenegro noted violaceous skin lesions, which progressed over a year to involve her legs, abdominal wall and nose. The lesions were confluent, and at least 1.0 cm thick, with *en cuirasse* involvement of her whole lower abdominal wall, and massive leg edema. After a positive biopsy for KS, cyclosporine was discontinued. During the following 6 weeks the KS partially regressed, but then relapsed, and PTX 60 mg/m^2/week was initiated. The KS regressed rapidly, and within 2 months a complete remission had occurred, with only residual hyperpigmentation. Her serum creatinine stabilized at 2.5 mg/dL on prednisone 5 mg/day. She remained in remission on bi-weekly treatment for 16 months, 30 months after onset of KS, with no significant toxicity. Although she remained tolerant of her graft, several medical problems developed which were due neither to chemotherapy nor her KS. Because of these, she preferred to discontinue PTX; 6 weeks later her diffuse cutaneous KS was relapsing.

Discussion

KS in post-renal transplant patients may be limited to one or a few cutaneous sites, disseminated to multiple cutaneous sites, or involve viscera. Some of these patients respond to the withdrawal of immunosuppressive therapy. Those who do not, and whose disease is cutaneous and localized, may be effectively treated with radiation (11). Persistent disseminated cutaneous disease, or visceral KS, require systemic therapy. Other groups have reported the results of chemotherapy in 23 such patients (12–18). All of those whose KS was limited to the skin responded completely to a variety of regimens, and survived. Half of the patients with visceral disease were refractory to systemic treatment and succumbed to KS. The efficacy of any treatment should therefore be evaluated separately for patients with cutaneous or visceral disease.

Because of the small numbers of patients treated with each regimen, it is difficult to confidently evaluate their relative efficacies (12–18). Bleo and etoposide, used as single agents, did not appear to be very effective (13,14,16). Of the seven patients with visceral KS treated with Dox–Bleo–vincristine (13), five responded and survived; Dox was probably the most active drug in this regimen. Renal transplant patients often have cardiac disease, and are therefore likely to have relative contra-indications to anthracycline therapy. Since only three patients were treated with PTX (15; our reports above), two of whom had exclusively cutaneous disease, it is difficult to draw conclusions concerning the efficacy of this agent for the treatment of post-renal transplant KS. There is, however, much more experience with its use in AIDS-related KS, including patients refractory to anthracyclines. In the most recent published series, response rates of 59–74% have been reported, with median response duration of 10.4 months and median survival of 15.4 months (11, 19). Weekly PTX is now first line therapy for AIDS-related KS at our medical center, where it is a common problem.

Post-transplant lymphoproliferative disease is more common than KS, and the larger experience in managing this problem is the basis for the general strategy for the treatment of virally induced neoplasia. The polyclonal form regularly regresses with the withdrawal of immunosuppressive treatment, but monoclonal large cell lymphomas also require multidrug chemotherapy. KS, whether sporadic, or related to immunodeficiency, progresses from polyclonal angoid hyperplasia and inflammation, to monoclonal lesions, in which spindle cells predominate (20). No analogous differences in the responses of poly- and monoclonal post-transplant KS to withdrawal of immunosuppressive therapy have been defined. The chemotherapy of virally induced neoplasms, such as AIDS or post-transplant lymphomas, and KS, remains empirical, and not related to the Epstein–Barr or HH8 viruses, which initiate cellular transformation. Virus-induced cell proliferation may be controlled by withdrawal of immunosuppressive therapy, or an increase in CD4 lymphocytes after effective antiretroviral treatment of AIDS. PTX was not chosen because of the specific histology of KS, but because it is a mitotic inhibitor, with an unusually broad spectrum of activity. Vinblastine, also a mitotic inhibitor, has long been the drug of choice in sporadic KS. However, when KS lesions become monoclonal the antiapoptotic protein product of the *Bcl-2* gene is over-

expressed, thus contributing to neoplastic progression. PTX inactivates the Bcl-2 protein, thus facilitating apoptosis, as well as inhibiting cell proliferation (20).

Further studies of weekly PTX, as first-line therapy for post-renal transplant KS refractory to withdrawal of immunosuppressive therapy, are indicated. We do not know how long PTX treatment should be continued after complete remission of post-transplant KS, though our experience with patient no. 2 suggests that complete responders are not necessarily cured. We cannot evaluate the risk of relapse in complete responders on maintenance PTX, if immunosuppressive therapy is resumed to avert impending graft rejection.

Acknowledgments

The authors thank Ms Victoria Maursky, Transplant Coordinator, for her invaluable assistance in patient care and data collection.

References

1. Penn I. Kaposi's sarcoma in organ transplant recipients. Transplantation 1981; 27: 8–11.
2. Frances C. Kaposi's sarcoma after renal transplantation. Nephrol Dial Transplant 1998; 13: 2768–2773.
3. Buonaguro FM, Tornesello ML, Beth-Giraldo E et al. Herpesviruses-like DNA sequences detected in endemic, classic, iatrogenic and epidemic Kaposi's sarcoma biopsies. Int J Cancer 1996; 65: 25–28.
4. Farge D, Lebbe C, Marjanovic Z et al. Human herpesviruses – 8 and other risk factors for Kaposi's sarcoma in kidney transplant recipients. Transplantation 1999; 67: 1236–1242.
5. Al-Sulaiman M, Haleem A, Al-Khader AA. Kaposi's sarcoma after renal transplant. Transplant Proc 1987; 19: 2243–2244.
6. Breier S, Lebedinsky C, Ayaviri C et al. Long-term weekly Taxol over one hour infusion with de-escalated premedication: a Phase II trial report. Breast Cancer Res Treat 1999; 57: 124.
7. Seidman AD, Hudis CA, Albanel J et al. Dose-dense therapy with weekly paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 1998; 16: 3353–3361.
8. Hussain S, Anderson DN, Salvatti ME et al. Onycholysis as a complication of systemic chemotherapy: report of five cases associated with prolonged weekly paclitaxel therapy and review of the literature. Cancer 2000; 88: 2367–2371.
9. Gill PS, Tulpule A, Espina BM et al. Paclitaxel as safe and effective in the treatment of advanced AIDS-related kaposi's sarcoma. J Clin Oncol 1999; 17: 1876–1883.
10. Luppi M, Barozzi P, Schulz TF et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. New Eng J Med 2000; 343: 1378–1385.
11. Krown SE, Myskowski PL, Paredes J. Medical management of AIDS patients with Kaposi's sarcoma. Med Clin North Am 1992; 76: 235–252.
12. Brambilla L, Boneschi V, Fossati S, Ferrscci S, Finzi AF. Vinoralbine therapy for Kaposi's sarcoma in a kidney transplant patient. Dermatology 1997; 194: 281–283.
13. Arican A, Karakayali H, Bilgin N, Haberal M. Results of treatment in renal transplant patients with Kaposi's sarcoma: One-center experience. Transplant Proc 2000; 32: 626.
14. Lesnoni La Parola I, Masini C, Nanni G, Diociaiuti A, Panocchia N, Cerimele D. Kaposi's sarcoma in renal transplant recipients: experience at the Catholic university in Rome. 1988–96. Dermatology 1997; 194: 229–233.
15. Wu CJ, Scadden DT. Posttransplant Kaposi's sarcoma treated with paclitaxel. J Clin Oncol 1998; 16: 3478–3479.
16. Ecder ST, Sever MS, Yildiz A et al. Kaposi's sarcoma after renal transplantation in Turkey. Clin Transplantation 1998; 12: 472–475.
17. Aebicher MC, Zala LB, Branthen LR. Kaposi's sarcoma as manifestation of immunosuppression in organ transplant recipients. Dermatology 1997; 195: 91–92.
18. Boehringer M, Schwarz A, Keller F. Kaposi's sarcoma after renal transplantation: treatment with liposomal doxorubicin. Nephrol Dial Transplant 1999; 14: 1342–1343.
19. Sgadari C, Toschi E, Palladino C et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus associated Kaposi's sarcoma. J Clin Oncol 1998; 16: 1112–1121.
20. Welles L, Saville W, Lietzau J et al. Mechanism of paclitaxel activity in Kaposi's Sarcoma. J. Immunology 2000; 165: 509–517.