Allogenic stem cell transplant in a patient with classical Kaposi’s sarcoma

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Abstract

A 68 year old male with a history of classical Kaposi’s sarcoma (KS) and precursor T-cell acute lymphoblastic leukemia (ALL) received an allogenic stem cell transplant from an unrelated donor to treat his ALL. He developed acute graft-vs.-host disease (GVHD) which was treated by increasing immunosuppressants. KS, which had been in remission for years, then recurred aggressively. Tapering immunosuppressants to treat the KS was not possible because of GVHD. Chemotherapy could not be used because of its adverse effect on the bone marrow so soon after transplant. The only option was to use antiviral therapy (cidofovir) to lower the level of HHV-8, the virus that is a causal factor in KS. Although HHV-8 levels were significantly reduced, new KS lesions continued to appear. The patient developed acute kidney injury after the third cidofovir infusion and died from renal and respiratory failure soon afterward. Post-mortem revealed extensive internal KS lesions involving multiple organs.

Based on the experience with this patient, allogenic transplant using an unrelated donor has been found to be a questionable treatment modality for classical KS patients requiring treatment for another condition such as leukemias and lymphomas. Post-transplant immunosuppression is required to prevent GVHD, and if it occurs, immunosuppression may have to be increased. Aggressive KS developed in this patient under these conditions, and could not be controlled by tapering immunosuppressants. Although the risk of GVHD is lower for an allogenic transplant using a matched sibling instead of an unrelated donor, the risk of both GVHD and aggressive KS both developing may still be unacceptably high.

Alternative treatment modalities for these patients might include continuing with chemotherapy and autologous transplant. These avoid GVHD and lower the need for long term immunosuppression, but have a much higher risk of relapse of the underlying malignancy. Still, they could be preferable to an allogenic transplant for such cases.

Introduction

Kaposi’s sarcoma (KS) is a relatively rare complication of stem cell transplants. It is more common in solid organ transplants where there is need for long term immunosuppression to prevent organ rejection. In allogenic stem cell transplants where there is a sibling or unrelated donor, a common complication is graft-vs.-host disease (GVHD) where the donor immune system attacks the host’s organs, commonly the skin and GI tract. This condition can be life threatening and requires immunosuppression to both prevent and control it.

HHV-8, a gamma herpes virus discovered by Chang and Moore in 1994, is recognized as
When the patient receiving an allogenic transplant is HHV-8 positive and requires immunosuppression to prevent or control GVHD, KS can result, although very infrequently. When it does, it is in most cases non-aggressive and can usually be treated by tapering immunosuppressants and using chemotherapy if necessary.1-6

The patient in this report also had a history of classical KS. This rather indolent disease mainly affects elderly Jewish and Italian men with normal immune systems. The KS that developed in this patient as a result of the immunosuppression required to control GVHD was found to be aggressive and uncontrollable.

There appear to be no reported cases of such patients in the medical literature. This report is presented in the hope that what was learned from the treatment of this patient will benefit future patients by allowing more informed treatment decisions.

Methods

An approval letter to use the patient’s autopsy report was obtained from the Director of Privacy Assurance at the Compliance & Privacy Office, Stanford University Medical Center, Palo Alto, CA. Written consent was also obtained from the patient's next of kin who also provided medical records.

History

The patient was a 68 year old male Ashkenazi Jew who was diagnosed in February 2012 with precursor T-cell acute lymphoblastic leukemia with complex cytogenetics. He also had a nearly two decade history of classical Kaposi's sarcoma (KS) which had been treated with antiviral therapy (acyclovir). The KS had been in continual remission except for a few outbursts of minor skin lesions which were treated by cryosurgery and intralesional velban injections. Over the next few months following his ALL diagnosis, he received hyper-CVAD and nelarabine chemotherapy, but failed to achieve remission on his first three inductions. Clofarabine was used for his fourth induction and he finally achieved a complete remission.

He received an allogeneic hematopoietic stem cell transplant at Stanford Hospital, Palo Alto, CA in late November 2012, and developed acute GVHD soon afterward involving the skin. In January 2013, he developed Legionella micadadei pneumonia involving the lower lobe of his left lung and was treated with levofloxacin. He also had flares of KS in the suprapubic and scrotal area, in addition to near the knees and on the hands. Immunosuppressants were tapered in an attempt to control the KS, but this worsened the GVHD which had by then involved the GI tract in addition to the skin. Immunosuppressants were then increased to control the GVHD, but new KS lesions
developed. Chemotherapy (e.g., doxil) could not be used because of its adverse effect on the bone marrow. In early March 2013, antiviral therapy (cidofovir) was started in an attempt to control the KS by lowering HHV-8 levels. He received three cidofovir infusions over a one month period which did reduce HHV-8 levels significantly, but new KS lesions continued to appear. The patient developed acute kidney injury several weeks after the third infusion. He was placed on palliative care and died in early May 2012 from renal and respiratory failure.

Post-mortem revealed in addition to moderate to severe KS lesions on the skin of the extremities and trunk with ulceration, extensive internal KS lesions in the small bowel, colon, liver, and right groin soft tissue. There was also probable KS involvement in the pancreas and spleen. Sections of kidney showed diffuse interstitial fibrosis, suggestive of previous tubulointerstitial injury. Cidofovir is known to induce kidney injury via tubular epithelial toxicity, and may have been a cause of this. However, tubulointerstitial nephritis can also occur in association with many other medications or systemic diseases.

Discussion

Allogenic transplant for this patient resulted in the development of aggressive KS when immunosuppression was required to control GVHD. No treatment was found which could control both conditions. His advanced age, adverse cytogenetics, and late achievement of remission increased the probability of GVHD developing.

It is well known that in AIDS, CD4-positive T-lymphocytes are destroyed by HIV and that aggressive KS develops in many AIDS patients that are both HHV-8 seropositive and leukopenic. It is especially necessary to suppress T-lymphocytes to control GVHD, hence this results in an environment where KS can develop in allogenic stem cell transplant patients if they are also HHV-8 seropositive. Yet for these patients, it is rare that KS develops even when immunosuppression is required to control GVHD. When KS does develop, it is generally not aggressive and can usually be treated by tapering immunosuppressants and using chemotherapy if necessary. But when the patient in this report who also had a history of classical KS was immunosuppressed, aggressive KS developed.

It was found that for this patient there was no level of immunosuppression where both GVHD and KS could be controlled. Chemotherapy could not be used so soon after transplant because of its adverse effect on the bone marrow. The only option was to use antiviral therapy to attempt to reduce HHV-8 levels with the hope that KS could be controlled. Cidofovir infusions did reduce HHV-8 levels but did not stop new KS
lesions from appearing on the skin. Acute kidney injury developed shortly after the third cidofovir infusion and progressed to renal failure and death.

**Conclusion**

For this patient, allogenic stem cell transplant led to GVHD and aggressive KS. It is not known how other classical KS patients receiving an allogenic transplant might fare, because of the absence of reported cases in the medical literature.

On this limited basis, allogenic transplant using an unrelated donor is a questionable treatment modality for classical KS patients requiring treatment for another condition such as leukemias and lymphomas. There is a high risk of GVHD developing with a concomitant risk of aggressive KS as GVHD is treated, and a lack of suitable options to control both conditions. Although the risk of GVHD developing is lower for an allogenic transplant using a matched sibling as compared with an unrelated donor, the risk may still be unacceptably high.

Depending on the underlying malignancy, alternative treatments for these patients might include continuing with chemotherapy and autologous transplant. These avoid GVHD and lower the need for long term immunosuppression, but have a much higher risk of relapse. Still, they could be preferable to an allogenic transplant for such cases.

**Acknowledgment**

The author wishes to thank Stanford Hospital for the use of information in the patient’s confidential autopsy report.

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