Published in final edited form as:

J Pediatr Hematol Oncol. 2009 February ; 31(2): 142–144. doi:10.1097/MPH.0b013e31819146e5.

Unusual Sites of Extraskkeletal Metastases of Ewing Sarcoma after Allogeneic Hematopoietic Stem Cell Transplantation

Christian M. Capitini, MD¹, Joanne Derdak, CRNP¹, Marybeth S. Hughes, MD², Cynthia P. Love, RN, BSN¹, Kristin Baird, MD¹, Crystal L. Mackall, MD¹, and Terry J. Fry, MD^{1,3}

¹Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States, 20892

²Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States, 20892

³Center for Blood and Cancer Disorders, Children's National Medical Center, Washington, DC, United States, 20010

Abstract

Allogeneic stem cell transplantation (SCT) for solid tumors remains under investigation. We report a case of extended disease stability after a non-myeloablative peripheral blood SCT for metastatic, refractory Ewing sarcoma. Of note, the patient developed metastatic disease to two unusual sites – the brain and small intestine. The allogeneic SCT environment may alter typical metastatic patterns, and may represent an ideal platform to manipulate and enhance the anti-tumor immune response. Further clinical trials are needed to evaluate the role for allogeneic SCT for this disease.

Current therapies for metastatic or relapsed Ewing sarcoma have not substantially improved outcomes in this high-risk population with five-year survival rates < 20% 1. Graft-versus-malignancy reactivity clearly contributes to the curative potential of allogeneic stem cell transplants (SCT) for leukemias and lymphomas, however the utility of allogeneic SCT for solid tumors remains controversial. Evidence for a graft-versus-tumor effect comes primarily from metastatic renal cell carcinoma 2, however responses have been reported in sarcomas, including a graft-versus-Ewing effect 3–6. Here we report a case of disease stability followed by an unusual pattern of recurrence in a Ewing sarcoma patient following reduced intensity allogeneic SCT.

A 26-year-old male initially presented with a 4-month history of left thigh pain and a palpable thigh mass. MRI revealed a 17 × 17cm mass arising from the left lateral femur, complicated by pathologic fracture. Needle biopsy revealed a Ewing sarcoma with no metastases noted on presentation. The patient received standard five-drug therapy (cyclophosphamide, doxorubicin and vincristine alternating with ifosfamide and etoposide) with local control consisting of 5580cGy radiation to the femur. At the completion of initial therapy there was no evidence of disease. One year later, a routine restaging chest CT revealed pulmonary metastasis and a left hilar lymph node (Figure 1A). The remainder of re-staging was negative including bone marrow biopsy. The patient received 4 cycles of cyclophosphamide and topotecan, during which time the pulmonary lesions progressed (Figure 1B). He was then enrolled on an IRB-approved, reduced intensity, allogeneic SCT protocol for patients with ultra-high risk pediatric sarcomas. Three cycles of induction

chemotherapy with EPOCH (etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide) were given for immune depletion and disease control, during which the pulmonary disease was stable with no new lesions. His preparative chemotherapy prior to SCT comprised of fludarabine, cyclophosphamide and melphalan followed by infusion of unmanipulated, G-CSF mobilized peripheral blood stem cells from a fully matched sibling on day +0. GVHD prophylaxis consisted of cyclosporine monotherapy. Myeloid engraftment occurred on day +10 with full donor chimerism by day +14. On day +19 he developed biopsy-proven acute GVHD of the skin and liver. Methylprednisolone was initiated, cyclosporine was discontinued, and tacrolimus was started. There was a complete response and methylprednisolone was tapered and discontinued on day +58, and tacrolimus was discontinued on day +91 (Figure 1C). During this time, CT scans of the chest revealed stable or shrinking lung nodules, although not sufficient to meet NCI RECIST criteria. However, biopsy confirmed the presence of active tumor. Lymphocyte reconstitution showed an initial rise at day +28, with a decrease in B and T cells during steroid administration, and then continued to recover after day +60 steadily (Figure 1D). Naïve and memory T cells demonstrated a similar decline with GVHD therapy followed by a rise in naïve CD4 T cells by day +100 that were sustained (Figure 1E).

Approximately three months post-SCT, the patient experienced a 15-minute seizure. A brain MRI demonstrated three hemorrhagic lesions consistent with metastases (Figure 2A). He subsequently received 2950cGy whole brain radiation with complete resolution of his lesions. Six months post-SCT, the left parenchymal and hilar metastases demonstrated very slow progression (Figure 1C) and he was placed on a 3-month trial of sirolimus for potential antitumor activity 7 and for management of limited, mucosal chronic GVHD. The patient had continued slow progression of pulmonary disease and at ten months post-SCT he received one cycle of reduced-dose EPOCH, complicated by anorexia, weight loss, and a one-month history of vague intermittent abdominal cramps with intermittent diarrhea. An abdominal CT revealed an ileocecal intusseption with a mass at the lead point (Figure 2B). He underwent ileocectomy, removing 20cm of ileum, and had a segmental resection of the mid-jejunum (Figure 2C). Surgical pathology showed his masses to be Ewing sarcoma. He received oral etoposide postoperatively, with no response, and subsequently died of progression on day +454 post-SCT.

We believe this case provides important observations regarding allogeneic SCT for Ewing sarcoma. First, reduced intensity conditioning is well tolerated in this high-risk patient population. Second, although Ewing sarcoma classically metastasizes to the lung, bone, and bone marrow, this patient recurred in two highly unusual metastatic sites, the brain and small intestine, following allogeneic SCT. Hematogenous brain metastases occur in as many as 40% of adult patients with solid malignancies but are uncommon in children with solid tumors, with one review reporting an incidence of 3.3% in Ewing sarcoma 8-9. Although there have been case reports of Ewing sarcoma occurring as a primary lesion of the small intestine, our review of the literature demonstrates this to be the first report of Ewing sarcoma metastasizing to the small intestine 10-13. Thus, we believe the occurrence of 2 highly unusual sites of metastasis in the same patient following allogeneic SCT may represent modulation of the disease by alloreactivity. While the timing of his metastases coincide with treatment of GVHD, which would suppress host immunity and perhaps allow metastases to sanctuary sites, there was also a period of relative stability of his pulmonary masses during the treatment of GVHD, despite pathologic confirmation of active tumor. Although this may be initially due to a conditioning regimen effect, the length of stability in a patient (218 days) who was previously rapidly progressing and refractory to salvage chemotherapy, suggests a degree of tumor control by the SCT. Interestingly, this progression occurred despite a very early recovery of naïve CD4⁺ T cells, which would be predicted to

contain a broad repertoire of specificity 14. Strategies to direct immune responses toward the tumor using vaccines may be ideal in this setting.

Alterations in metastatic patterns may be due to prolonged survival, alteration of the host environment or the introduction of the donor immune response, forcing the tumor to escape in unusual sites. Allogeneic SCT may represent a platform from which to manipulate and enhance the anti-tumor immune response. Whether this offers an inherent advantage over approaches to induce an autologous anti-tumor immune response remains to be seen 15.

Acknowledgments

This work was funded by the Intramural Research program at the National Institutes of Health.

References

- Bernstein M, Kovar H, Paulussen M, et al. Ewing's Sarcoma Family of Tumors: Current Management. *Oncologist*. 2006; 11:503–519. [PubMed: 16720851]
- Ueno NTNT, Childs RWRW. What's past is prologue: lessons learned and the need for further development of allogeneic hematopoietic stem cell transplantation for renal cell carcinoma. *Biology of blood and marrow transplantation*. 2007; 13:31–33. [PubMed: 17222750]
- Bregni M, Bernardi M, Ciceri F, Peccatori J. Allogeneic stem cell transplantation for the treatment of advanced solid tumors. *Springer Seminars in Immunopathology*. 2004; 26:95–108. [PubMed: 15378271]
- Burdach S, van Kaick B, Laws HJ, et al. Allogeneic and autologous stem-cell transplantation in advanced Ewing tumors: An update after long-term follow-up from two centers of the European Intergroup Study EICESS. *Ann Oncol*. 2000; 11:1451–1462. [PubMed: 11142486]
- Koscielniak E, Gross-Wieltsch U, Treuner J, et al. Graft-Versus-Ewing Sarcoma Effect and Long-Term Remission Induced by Haploidentical Stem-Cell Transplantation in a Patient With Relapse of Metastatic Disease. *J Clin Oncol*. 2005; 23:242–244. [PubMed: 15625381]
- Lucas K, Schwartz C, Kaplan J. Allogeneic stem cell transplantation in a patient with relapsed Ewing sarcoma. *Pediatric Blood & Cancer*. 2008; 51:142–144. [PubMed: 18266223]
- Wan X, Helman LJ. The Biology Behind mTOR Inhibition in Sarcoma. *Oncologist*. 2007; 12:1007–1018. [PubMed: 17766661]
- Curless RG, Toledano SR, Ragheb J, Cleveland WW, Falcone S. Hematogenous brain metastasis in children. *Pediatric Neurology*. 2002; 26:219–221. [PubMed: 11955930]
- Simpson RK, Bruner JM, Leavens ME. Metastatic ewing's sarcoma to the brain: case report and review of treatment. *Surgical Neurology*. 1989; 31:234–238. [PubMed: 2922669]
- Adair AA, Harris SSA, Coppin MMJ, Hurley PPR. Extraskeletal Ewings sarcoma of the small bowel: case report and literature review. *Journal of the Royal College of Surgeons of Edinburgh*. 2001; 46:372–374. [PubMed: 11768578]
- Batzliou CC, Stathopoulos GGP, Petraki KK, et al. Primitive neurectodermal tumors: a case of extraosseous Ewing's sarcoma of the small intestine and review of the literature. *Journal of BUON*. 2006; 11:519–522. [PubMed: 17309187]
- Boehm R, Till H, Landes J, Schmid I, Joppich I. Ileoileal Intussusception Caused by a Ewing Sarcoma Tumour. An Unusual Case Report. *European Journal of Pediatric Surgery*. 2003:272–275. [PubMed: 13680499]
- Shek T, Chan G, Khong P, Chung L, Cheung A. Ewing sarcoma of the small intestine. *J Pediatr Hematol Oncol*. 2001; 23:530–532. [PubMed: 11878783]
- Hakim FT, Memon SA, Cepeda R, et al. Age-dependent incidence, time course, and consequences of thymic renewal in adults. *The journal of clinical investigation*. 2005; 115:930–939. [PubMed: 15776111]
- Dagher R, Long LM, Read EJ, et al. Pilot trial of tumor-specific peptide vaccination and continuous infusion interleukin-2 in patients with recurrent Ewing sarcoma and alveolar

rhabdomyosarcoma: An inter-institute NIH study. *Medical and Pediatric Oncology*. 2002; 38:158–164. [PubMed: 11836714]

Figure 1.

Pulmonary metastases to the left hilum and left lower lobe as shown by chest CT post-contrast, (A) starting at initial recurrence, and (B) at pre-SCT restaging after 4 cycles of cyclophosphamide and topotecan. (C) Followed over the length of the SCT, a substantial period of disease stability is noted when examining the longest diameter of the pulmonary lesions. (D) Immune reconstitution of T cells ($CD3^+$, $CD4^+$ and $CD8^+$), $CD20^+$ B cells and $CD16^+$ $CD56^+$ natural killer cells during the SCT period as determined by flow cytometry of peripheral blood lymphocytes. (E) Immune reconstitution of memory $CD4^+$ T cells ($CD45RO^+$), naïve $CD4^+$ T cells ($CD45RA^+$ $CD62L^+$), memory $CD8^+$ T cells ($CD45RO^+$), and naïve $CD8^+$ T cells ($CD28^+$ $CD57^+$) during the SCT period as determined by flow cytometry of peripheral blood lymphocytes.

Figure 2. Ewing sarcoma metastases (A) to the left parietal lobe and right occipital lobe as visualized by MRI T2 post-FLAIR, (B) serving as a lead point for an ileocecal intussusception seen by abdominal CT post-contrast (C), and during exploratory laparotomy.