Published in final edited form as:

Pediatr Blood Cancer. 2008 April ; 50(4): 737–738. doi:10.1002/pbc.21364.

Can Less Really Be More? Using Lessons From Leukemia and Cancer Stem Cells to Make Sense of Oral Maintenance for Metastatic Sarcoma

Timothy P. Cripe, MD, PhD*

Division of Hematology/Oncology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 3333 Burnet Ave., Cincinnati, Ohio 45229

If a little is good, it stands to reason a lot is better. In fact, the steep dose–response curve of most anticancer drugs is well known [1], hence the nearly ubiquitous central venous catheter. But when it comes to the treatment of metastatic solid tumors, with the notable exception of neuroblastoma [2], unexpectedly more, in fact, is not panning out to be better. One-by-one the list of metastatic solid tumors responding to megadose therapy made possible by hematopoietic stem cell rescue continues to shrink, deflating our hopes of being rescued by our marrow transplant colleagues and prompting calls for novel ideas [3]. Might one of those “new” ideas be found in the acute lymphoblastic leukemia (ALL) playbook, oral maintenance?

Enter stage left the German Cooperative Weichteilsarkomstudie. While the luster of high dose therapy (HDT) was still alluring, they designed the CWS 96 trial to compare HDT to oral maintenance treatment (OMT), reported in this issue of *Pediatric Blood & Cancer*. Talk about David versus Goliath! Given the fact that antiangiogenic metronomic dosing was still a twinkle in Dr. Folkman's eye [4], the idea of using OMT for metastatic sarcoma was, to use the definition of “novel” from the online etymology dictionary (www.etymonline.com), certainly “strange and unusual.” In fact, finding 51 subjects to take low-dose pills instead of intravenous therapy, especially at that time as part of up-front therapy, could be considered astonishing!

As I've heard happens with the stock market, sometimes risks lead to payoffs. Klingebiel et al. report superior results using OMT compared to HDT. As they point out in their discussion, the fact that HDT was not helpful for metastatic soft tissue sarcoma is no longer a surprise. The results with OMT, however, are nothing short of remarkable. With a median follow-up of nearly 5 years, the overall survival of patients treated with OMT was double that seen with patients given HDT, and for patients with rhabdomyosarcoma survival was tripled. Unfortunately, neither treatment strategy was helpful for patients with bone or bone marrow involvement.

Are the results believable? Although intriguing, the study is full of limitations and caveats; as with any surprise, further data are needed to be convincing. For example, the low completion rate is of concern: out of 295 patients enrolled, only 96 (32.5%) completed the study. Perhaps this low number reflects the difficulties of managing a clinical trial at 50 different sites in 5 different countries. In addition, investigators and patients may have opted to diverge from the study because there is no clear standard of care for these patients. Also,

*Correspondence to: Timothy P. Cripe, Division of Hematology/Oncology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 3333 Burnet Ave., Cincinnati, OH 45229. timothy.cripe@cchmc.org.

the bias naturally introduced by making the study assignment dealer's choice is an issue, though the similarities between groups is reassuring. Finally, the inclusion of multiple histologies is a confounding variable.

Counterintuitive results are easier to accept if there is a sensible explanation. Can our experience with maintenance of leukemia remission shed some light? The rationale for maintenance therapy in ALL is mostly empiric: outcome is worse without it. The reasons maintenance therapy is thought to be effective in ALL are multifactorial, including continued cytoreduction, prevention of the emergence of drug-resistant clones, and drug exposure when quiescent leukemic cells exit G_0 , a time they should be most susceptible to antimetabolites [5]. The fact that angiogenesis also plays a role in the growth of ALL blasts [6] may be an additional mechanism given the fact that maintenance chemotherapy is essentially metronomic. Whether these explanations apply to OMT for sarcomas is unclear. In the absence of a rational explanation for OMT, it will be difficult to refine therapy, other than with clinical "trial and error."

What makes metastatic disease so difficult to cure? Here the answer may very well lie in the stem cell; again, lessons from the study of leukemia are potentially helpful. Considerable evidence supports the hypothesis that most leukemias arise from an early stem or progenitor cell, in an analogous fashion to the process of normal hematopoiesis [7]. There are now mounting data supporting the stem cell theory of cancer for solid tumors as well [8]. Although thousands to millions of unselected cancer cells are often required to form tumors in xenograft models, most cancers are heterogenous, and only a small subpopulation of cells are actually tumorigenic. Similar to normal stem cells that give rise to mixed types of differentiated cells, tumorigenic stem cells are capable of generating a diverse, mixed tumor cell population that recapitulates the original cancer. For example, in one study <100 cells of the identified tumorigenic subpopulation in a breast cancer model were required to form tumors [9]. Highly tumorigenic cells have also been described in other cancers such as brain tumors [10], melanoma [11], hepatocellular carcinoma [12] and neuroblastoma [13]. Although a recent study questioned the use of xenograft models for these tumorigenicity studies [14], the fact that only a subset of tumor cells are efficient at establishing a tumor is undeniable. This emerging stem cell theory of cancer suggests that cancer relapse, and even metastasis, may be caused by a rare tumorigenic progenitor cell that is relatively resistant to conventional chemotherapy. The theory neatly explains the need for local control of sarcomas: surgical removal and radiation therapy (for some histologies) may be the only reliable methods available to effectively target the cancer stem cell.

Is it possible that OMT targets cancer stem cells, explaining the CWS 96 study results? Certainly the antiangiogenic effects of OMT might affect cancer stem cells; however, a canonical feature of stem cells is relative resistance to hypoxia, and hypoxia has been shown to upregulate cancer stem cell-specific signaling pathways [15]. In support of this possibility is the prevailing theory that the solid tumor stem cell [3] niche [2] is perivascular, and one study suggests antiangiogenics affect stem cells by destroying that niche [16]. "Catching" cancer stem cells when they exit G_0 is also not likely, as these cells are typically multidrug resistant [16]. The lack of an adequate scientific explanation for the superior results of OMT therapy further begs for confirmatory studies.

Even if the encouraging results of the Klingebiel et al. study are upheld, curing only half of patients is obviously not good enough. With the ever-deafening call for new druggable targets, identification and study of cancer stem cells in sarcomas is paramount. If the theory is true, and the real purpose of local control is to eliminate the cancer stem cell, improved cure rates for metastatic sarcomas will likely only be achieved if we can target these insidious intruders and thereby provide adequate "systemic" local control.

References

1. Adamson, P.; Balis, F.; Berg, S., et al. General principles of chemotherapy. In: Pizzo, P.; Poplack, D., editors. Principles and practice of pediatric oncology. 5. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. p. 290-365.
2. Matthay K, Villablanca J, Seeger R, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Engl J Med 1999;341:1165–1173. [PubMed: 10519894]
3. Snyder KM, Mackall CL. Therapy for metastatic ESFT: is it time to ask new questions? Pediatr Blood Cancer 2007;49:115–116. [PubMed: 17474114]
4. Browder T, Butterfield CE, Kraling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 2000;60:1878–1886. [PubMed: 10766175]
5. Margolin, J.; Steuber, C.; Poplack, D. Acute lymphoblastic leukemia. In: Pizzo, P.; Poplack, D., editors. Principles and practice of pediatric oncology. 5. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. p. 538-590.
6. Perez-Atayde AR, Sallan SE, Tedrow U, et al. Spectrum of tumor angiogenesis in the bone marrow of children with acute lymphoblastic leukemia. Am J Pathol 1997;150:815–821. [PubMed: 9060819]
7. Luo L, Han ZC. Leukemia stem cells. Int J Hematol 2006;84:123–127. [PubMed: 16926133]
8. Polyak K, Hahn WC. Roots and stems: stem cells in cancer. Nat Med 2006;12:296–300. [PubMed: 16520777]
9. Al-Hajj M, Wicha MS, Benito-Hernandez A, et al. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 2003;100:3983–3988. [PubMed: 12629218]
10. Singh SK, Clarke ID, Terasaki M, et al. Identification of a cancer stem cell in human brain tumors. Cancer Res 2003;63:5821–5828. [PubMed: 14522905]
11. Fang D, Nguyen TK, Leishear K, et al. A tumorigenic subpopulation with stem cell properties in melanomas. Cancer Res 2005;65:9328–9337. [PubMed: 16230395]
12. Suetsugu A, Nagaki M, Aoki H, et al. Characterization of CD133+ hepatocellular carcinoma cells as cancer stem/progenitor cells. Biochem Biophys Res Commun 2006;351:820–824. [PubMed: 17097610]
13. Ross RA, Spengler BA. Human neuroblastoma stem cells. Semin Cancer Biol 2007;17:241–247. [PubMed: 16839774]
14. Kelly PN, Dakic A, Adams JM, et al. Tumor growth need not be driven by rare cancer stem cells. Science 2007;317:337. [PubMed: 17641192]
15. Keith B, Simon MC. Hypoxia-inducible factors, stem cells, and cancer. Cell 2007;129:465–472. [PubMed: 17482542]
16. Folkins C, Man S, Xu P, et al. Anticancer therapies combining antiangiogenic and tumor cell cytotoxic effects reduce the tumor stem-like cell fraction in glioma xenograft tumors. Cancer Res 2007;67:3560–3564. [PubMed: 17440065]
17. Donnenberg VS, Donnenberg AD. Multiple drug resistance in cancer revisited: the cancer stem cell hypothesis. J Clin Pharmacol 2005;45:872–877. [PubMed: 16027397]