

## Pediatric Oncology Drug Development: A Case Report and Pathways Forward

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### Abstract

In this case report, we briefly review the treatment of a patient with metastatic, refractory Ewing's sarcoma who was treated on a Phase I clinical trial before she died from progressive disease. The case illustrates the need for early phase clinical trials programs in pediatric oncology, and the way in which investigators approach such programs.

**Keywords:** Ewing's sarcoma; Orthopedic oncology

### Case

In April of 2013, a 15 year old Caucasian female from Trinidad presented to orthopedic oncology in Miami with a right sided buttock mass. Biopsy demonstrated Ewing's sarcoma without evidence of any characteristic translocations involving EWS. MRI suggested a soft tissue primary lesion. Subsequent staging studies revealed numerous lung metastases, involvement of the ipsilateral iliac bone, and FDG uptake on PET CT at S1. As there were no open studies at the time for children with metastases outside of the lungs for Ewing's sarcoma, she began treatment with standard compression chemotherapy every two weeks, with cycles of vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide and etoposide. She had mild hand foot syndrome during this time, and after four cycles, CT scan of the chest revealed progression in size and number of lung metastases. Her primary tumor was no smaller, but was slightly necrotic centrally as seen on MRI. Subsequently, her chemotherapy was changed to topotecan and cyclophosphamide, and four cycles of this were given, concurrently with radiotherapy to her primary tumor. The lesions in her lungs continued to increase in number and the individual lesions continued to grow on this second line of therapy. She was then offered participation in a Phase I Sunshine Project Trial combining vincristine/irinotecan/temozolomide (VIT) with metformin (NCT01528046). After two cycles of this regimen, including metformin in the second cycle, CT scans again demonstrated increase in number and size of lung metastases from before study therapy was initiated. She was removed from protocol therapy with a plan to have her undergo palliative lung irradiation, while a search for further clinical trials options was undertaken. Her primary tumor had been radiated and had stopped growing, suggesting some sensitivity to chemotherapy in combination with radiation therapy. Her major toxicities from therapy at this point included hemorrhagic cystitis, thought to be due to a combination of prior alkylator therapy and thrombocytopenia, and peripheral neuropathy from vincristine. However, she began complaining of headache during this time, and rapidly became debilitated with visual complaints and difficulty walking. Imaging of her brain revealed intraparenchymal brain

metastases with hemorrhage and edema despite her treatment with CNS penetrating chemotherapy. She was transferred to a hospital closer to her home and expired soon thereafter from progressive brain metastases, in December of 2013.

### Ewing's Sarcoma

Ewing's sarcoma, or Ewing's family of tumors, is the second most common bone cancer in children. Great strides have been made in the treatment of patients with Ewing's sarcoma, particularly for children with localized disease at presentation, for whom intensified, 5 drug alternating chemotherapy with aggressive local control has yielded a 5 year event free survival of 76 % [1]. However, despite novel chemotherapeutic strategies employing new agents such as topotecan on top of the most successful treatment backbone (NCT01231906), it is likely that there will be a plateau in the disease benefit associated with intensified chemotherapy for children with Ewing's sarcoma. For children with metastatic disease at presentation, the situation is only worse. This situation mirrors that in many pediatric cancers, hence the crucial need to study new agents in pediatric cancer [2]. For adolescents and young adults with this disease, the rate of progress has been particularly slow [3]. The search for new agents includes efforts to combine novel targeted therapies, immunotherapies and epigenetic modifiers to take advantage of particular biology in these tumors, utilize new findings regarding the immune system in cancer, and overcome resistance to standard treatment.

### Rationale for Pediatric Oncology Phase I Programs

For children with refractory or relapsed cancer, access to experimental clinical trials provides hope to families, allows for more rapid learning about new therapies in children with cancer, and holds some prospect of direct benefit to patients. Most early phase clinical trials in children with cancer are modeled on some body of work in adults with cancer, so dose levels tend to be more likely to be biologically active. Early phase clinical trials for children with cancer are localized at centers belonging to a handful of groups specializing in such studies. The University of Miami belongs to the Sunshine Project, a group dedicated to the development and conduct of experimental treatment in children with cancer. Had our patient been treated

outside of a region where a phase I program existed, or in her native country, she would not have had access to a phase I study. Even if she were treated with the same, informed salvage regimens she received in Miami, we would not have learned about new therapies from her care if she were not enrolled on a study. This learning about new agents is crucial for progress towards curative or at least clinically beneficial therapy in children with cancer. Without initial trials testing agents such as temsirolimus, metformin or epigenetic modifiers in combinations for children with cancer, in order to demonstrate safety and early data regarding efficacy, these agents cannot be moved into front line or first relapse trials [4].

Phase I trials in pediatric oncology depend on relevant discoveries in the laboratory, access to experimental agents, motivated and capable investigators, and the research infrastructure to translate important opportunities into the clinic. Traditionally, in North America, most early phase clinical trials in pediatrics were run through the crucial National Cancer Institute (NCI) supported Children's Oncology Group (COG) phase I consortium. While this critical group has been and continues to be the largest early phase clinical trials program in pediatric oncology, several other groups have joined the effort over the years. These groups bring crucial expertise in relevant disease specific areas, e.g. New Approaches to Neuroblastoma Therapy (NANT) and Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL), coupled in some cases with complementary geographic coverage, e.g. The Sunshine Project in Florida. Clearly for this patient, who was enrolled on one phase I study but was unable to receive any further study therapy beyond the VIT metformin study, the opportunity to enroll on a Sunshine Project study was important, and for the scientific community, her enrollment meant that we were able to learn something from her unfortunate situation. We need even more options for children with refractory cancer, and more effective strategies that can be employed earlier in the disease course for children with poor risk features or poor response to therapy. This case also suggests the potential value for incorporation of radiation therapy into early phase clinical trials, although the toxicity of multi-modality therapy may complicate safety evaluations in studies intended to demonstrate this.

The evaluation of metformin in the context of pediatric cancer is important for two reasons. First, type two diabetes is becoming increasingly common in children in North America and other developed areas. It is becoming more frequent for children diagnosed with cancer to have a pre-existing diagnosis of diabetes and be on stable dosing of metformin. Understanding the safety of this drug in the context of multi-modality therapy for cancer in children is important [5] and the two phase I trials in the Sunshine Project employing metformin should help address this situation. Second, there are numerous studies suggesting that metformin improves the survival of patients with cancer [6] and specific instances of metformin being effective in vitro against models of pediatric cancer [7]. This anti-cancer effect of metformin is thought to be mediated through several putative mechanisms, including via AMP kinase signaling, which potentially synergizes with mTOR inhibition.

New agents for combination in pediatric oncology exist. The difficulty is in matching the opportunities to the diseases. For instance, there is interest in employing histone deacetylase (HDAC) inhibitors in Ewing's sarcoma combination therapy [2]. Vorinostat, an older generation HDAC inhibitor, has some modest activity when tested in pre-clinical combinations against pediatric cancer [8]. Entinostat, a newer HDAC inhibitor, has been shown to improve the antigenicity of

Ewing's sarcoma in the laboratory, has activity against osteosarcoma in pre-clinical models, and has been associated with clinical benefit when given as a single agent in an adult with Ewing's sarcoma [9-11]. The task now remains to create a protocol that allows for testing of this agent in children with solid tumors.

## Summary

Early phase clinical trials for children with relapsed or refractory cancer provide crucial hope for families, and advance our knowledge of new treatments in such patients. Such trials can even help to formulate new standards for up front or salvage therapy. For instance, through the work of TACL, new insight into the potential of bortezomib in pediatric hematological malignancies was revealed [12]. To be accessible, such trials need to be broadly geographically available and have reasonable eligibility criteria. At the same time, they need to be informed by the latest clinical and laboratory science, which can come from the literature, from individual laboratories acting in support of a particular study or from large scale translational efforts such as the Pediatric Pre-clinical Testing Program [13]. Although targeted agents hold great promise for the future of cancer treatment, strategies that are likely to be successful in the near term will employ rationale combinations of therapy that approach one or more of the emerging hallmarks of cancer [2,14]. Large groups supported by the NCI, closely aligned with major pre-clinical efforts are key to the development of new drugs. At the same time, smaller groups can provide geographic coverage for enrollment in early phase clinical trials, and outlets for smaller laboratories approaching pediatric cancer from a different of angles. Such groups can still translate pre-clinical findings from completed studies to the larger pediatric oncology community. Bortezomib has now become part of the COG relapsed leukemia program, for instance. (NCT00077467) Both approaches to phase I trials in pediatric oncology are important, and since both NCI and non-NCI supported groups may complement each other, both are worthy of support financially and intellectually. No phase I efforts will ultimately be successful without the participation of the patients and their families, for whom we must continue our work until curative therapy becomes a possibility for all children with cancer.

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