July 9, 2015

From: David A. Jacobsohn, MD, ScM

Chief, Division of Blood and Marrow Transplantation, Children's National Health System

To: Rosemary Schnall
1650 Market Street | One Liberty Place, Suite 1800 | Philadelphia, PA 19103-7395

RE: Michael Pulaski (administrator of estate of Sarah Pulaski v Children's Hospital of Philadelphia)

Expert Opinion

I have reviewed the following documents: Complaint, medical records (inpatient and outpatient) of Sarah Pulaski, depositions of Michael Pulaski, Rene Paradis, Dr. Balis, Dr. Wood, Dr. Rheingold, Dr. Bunin, Dr. Aplenc, Dr. Leahey, Dr. Evageliou, blogs, emails. AALL0434 Protocol, Dr. Sanders' expert and medical literature cited in her report.

Clinical Course

Sarah Pulaski was diagnosed at age 9 years, with T-cell ALL on 1/3/2010, with a White Blood Cell Count of >500,000 and CNS involvement (CNS2a). She had a cytogenetic abnormality of her blasts (t8:14). On January 4, 2010, Sarah's parents met with Dr. Varela, Dr. Wray and a social worker to discuss Sarah's condition and Sarah's participation in clinical trial AALL0434 Intensified Methotrexate, Nelarabine and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia Part I. Following a detailed discussion regarding Sarah's diagnosis, prognosis, plan of treatment, risks and alternatives, Ms. Paradis gave written consent for Sarah's participation in Part I of the clinical trial AALL0434. Sarah began 4-drug induction chemotherapy on 1/4/10 (vincristine, daunomycin, prednisone, peg-asparaginase) on the ALL0434 study.

Given Sarah Pulaski's initial slow response to treatment, Dr. Rheingold spoke to the family about possibility of a bone marrow transplant in the event Sarah was an induction failure. In that event, which did not in fact occur, a bone marrow transplant would have been one treatment option. Also discussed was Sarah's brother having HLA typing to determine whether he would be a suitable donor, in the event Sarah needed a transplant.

Case ID: 130802504
Control No.: 15082046

Fortunately, on day 29, a bone marrow aspirate after induction showed that Sarah was in complete morphologic remission (0% morphologic blasts) but Sarah had 3.3% minimal residual disease (MRD) by flow.

Sarah was classified as high risk per the AALL0434 study due to an MRD ≥ 1% on Day 29. On February 5, 2010, the parents met with Dr. Evageliou and he explained Part II of the clinical trial AALL0434, the various treatment arms, risks and alternatives to the study. He reviewed the detailed written consent with the parents. Ms. Paradis gave written consent for Sarah's participation in Part II of the clinical study. Sarah was randomized to arm D (2/5/2010) which includes high dose methotrexate and nelarabine. During consolidation she received nelarabine, intrathecal methotrexate, cyclophosphamide, cytarabine, 6-MP, vincristine, Peg-Asparaginase (augmented BFM backbone). The main aims are to determine, through randomization, the relative safety and efficacy of the addition of nelarabine to augmented BFM therapy (Regimen C, CCG-1961) and to determine the relative safety and efficacy of high dose methotrexate (5 g/m2) with leucovorin rescue compared to escalating methotrexate without leucovorin rescue plus Pegaspargase (Capizzi I) delivered during Interim Maintenance.

Dr. Rheingold and Dr. Wood spoke to the family about evaluating Sarah for MRD at the end of consolidation. If Sarah was MRD positive at the end of consolidation, Sarah would be referred to BMT for a possible transplant. Sarah's brother underwent HLA typing in March 2010 and subsequently, he was determined to be a matched donor.

Sarah underwent an end of consolidation bone marrow aspirate on 5/20/10 and that showed 0% blasts by morphology and 0% MRD by flow. Sarah was in complete morphologic and molecular remission and appropriately remained on the clinical trial.

Sarah then began interim maintenance 5/20/10 and delayed intensification on 9/13/10. The second portion of delayed intensification was delayed until 11/18/10 given slow recovery of counts.

As per study, she received prophylactic cranial irradiation (12 Gy) during delayed intensification.

On 3/21/2011, Sarah had an early CNS relapse and underwent mitoxantrone/vincristine/Dexamethasone chemotherapy. The plan was to do 2 cycles followed by an allogeneic bone marrow transplant from HLA-identical sibling. However, she was MRD positive at 3.1% after 1 cycle. She was referred to St. Jude for experimental therapy (NK cells) but died of infection during the chemotherapy prep for this protocol.

It is my opinion that the medical decision making and care provided to Sarah Pulaski by her treating physicians was appropriate and met the standard of care in this case. Appropriate informed consent was obtained for Sarah's participation in Part I and Part II

Case ID: 130802504
Control No.: 15082046

of AALL0434. The treatment, risks and alternatives to this study were appropriately and fully discussed with the parents. The written consents signed by Rene Paradis, along with the e-mails and blogs, establish the parents were appropriately consented. A bone marrow transplant was not an alternative treatment for Sarah Pulaski at the time the consents were obtained for participation in Part I and Part II of the clinical trial AALL0434.

I reviewed the report of Dr. Sanders. I agree with Dr. Sanders in that the informed consent documents contain all the required elements of consent. I disagree with Dr. Sanders' opinion that referral to a BMT consult was warranted at that time of 1st remission. Transplantation was not an appropriate alternative option for Sarah at 1st remission. Moreover, the studies cited by Sanders are not applicable for myriad reasons.

The main question is whether this patient should have been referred to bone marrow transplantation in 1st remission. First, members of CHOP's BMT team participated in, and had active input at, the HMG Conferences during which time the plan of care and treatment for Sarah Pulaski was discussed and formulated. Given the inherent risks (GVHD, infection) of bone marrow transplantation with transplant-related mortality 10%-20% and relapse rates of 20%-30% after transplant (refs: Tracey et al, Transplantation conditioning regimens and outcomes after allogeneic hematopoietic cell transplantation in children and adolescents with acute lymphoblastic leukemia, Biol Blood Marrow Transplant. 2013 Feb;19(2):255-9. Zhang et al, Comparison of outcomes after HLA-matched sibling and unrelated donor transplantation for children with high-risk acute lymphoblastic leukemia, Biol Blood Marrow Transplant. 2012 Aug;18(8):1204-10, Shaw et al, Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors, Blood. 2010 Nov 11; 116(19): 4007–4015), transplant is reserved for when the likelihood of relapse based on available information is so high that it is worth subjecting the patients through the potentially very high-risk procedure. The standard of care in pediatric acute lymphoblastic leukemia for transplant in 1st remission are: primary induction failure, persistent MRD after consolidation, extreme hypodiploidy, infants with MLL rearrangements and <6 months of age (refs: Pulsipher et al, High Risk Pediatric Acute Lymphoblastic Leukemia: To Transplant or Not to Transplant?, Biol Blood Marrow Transplant. 2011 January ; 17(1 Suppl): S137–S148; Oliansky et al, Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Pediatric Acute Lymphoblastic Leukemia: Update of the 2005 Evidence-Based Review, Biol Blood Marrow Transplant 18: 505-522 (2012) . Sarah had none of these conditions and therefore, Sarah did not meet well accepted criteria for transplant in 1st remission. It was not the standard of care to refer Sarah to the BMT team for transplantation when she was in first remission.

To assess the quality of the decisions made in this case and attempt, it is important to look at modern literature (1990s and ahead) and literature where similar chemotherapy was employed as to what this patient received. While tempting, it is also important not to

Case ID: 130802504
Control No.: 15082046

overly focus on transplant-only publications which only report results of patients that went to transplant and therefore may have an element of bias (since they report on patients that were well enough to undergo transplant). Transplant-only papers do not provide information comparing the outcomes of children who undergo transplant versus those who are treated with chemotherapy alone.

With modern chemotherapy (ie augmented BFM) the risk of relapse in a patient with T-cell ALL who achieves a 1st complete remission is up to 20% depending on risk (Schrappe et al, Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study, Blood 25 Aug 2011)). The risks of mortality and morbidity of a transplant outweigh the benefits. Therefore, it is not the standard of care to refer these patients to transplant.
Dr. Sanders claims that Sarah should have been referred for consultation for marrow transplantation during Interim Maintenance. I disagree. Chemotherapy commonly causes count suppression resulting in chemotherapy being held until counts recover to acceptable levels. Although Sarah did experience count suppression on several occasions resulting in her chemotherapy being held until her counts recovered, this was neither an indication for a referral to BMT team, nor an indication for a transplant. The risks of mortality associated with transplant outweighs the potential benefit.

One of the most relevant publications to refer to in this case is: "Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study" by Schrappe et al, Blood 2011. This is extremely relevant because: a) it is a large number of children all with T-cell ALL, prospectively followed (N=464); b) many of the patients were on BFM regimen (which is the backbone used in the COG protocol the patient was enrolled on); and c) MRD was done at systematic timepoints to determine the prognostic value of MRD. The 7-year estimates of overall survival were 80.7%. In this study, MRD was done at induction (TP1) and consolidation (TP2) and patients were called standard-risk if MRD was negative at both, intermediate risk if positive at one or both but <0.001 at TP2, and high risk if MRD>0.001 at TP2.

When they looked at outcomes the overall survival for standard was 91%, intermediate 80.6% and high risk 49.8% (at 7 years). By cumulative incidence of relapse, it was 7.6% for standard, 17.6% for intermediate, and 37.7% for high risk (at 7 years).

Case ID: 130802504
Control No.: 15082046

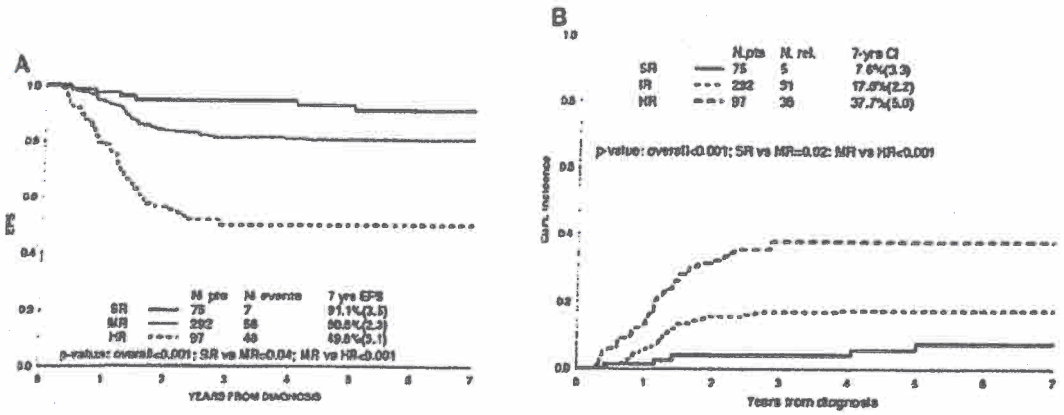

Figure 2. Treatment outcome in risk groups. EFS (A) and cumulative incidence of relapse (B) according to PCR-based MRD classification in 484 patients

The authors indicate that in 48% of patients where TP1 was positive, TP2 became negative, and MRD at TP2 "constitutes the most important predictive factor for relapse in childhood T-ALL" and "early TP1 MRD levels were irrelevant if MRD at TP2 was negative."

Based on this study, Sarah Pulaski would have been classified as intermediate risk and the MRD at TP2 supersedes all other features in terms of prognosis. This means that after taking into account MRD at TP2, the effect of high white blood cell count at diagnosis falls off. Sarah had a 80% likelihood of event-free-survival using this backbone of chemotherapy.

Furthermore, on the ALL0434 study the patient was randomized to receive nelarabine, an agent with strong anti-T cell leukemia effect; therefore, the study aims to identify if results long-term could be even better than that.

Based on Sarah Pulaski's negative MRD after consolidation, even with chemotherapy being held on several occasions until count recovery, it is my opinion with a reasonable degree of medical certainty that Sarah Pulaski was not a transplant candidate while in 1st remission.

If a patient relapses and achieves a 2nd CR, transplant is indicated because the chance of a further relapse is unacceptably high. Unfortunately, Sarah did not achieve a second remission. Therefore, it is my opinion to reasonable degree of medical certainty that Sarah Pulaski was not a candidate for transplant when she relapsed because she did not attain a 2nd remission.

Case ID: 130802504
Control No.: 15082046

Mr. Pulaski contends that in late July or early August 2010, he told Dr. Wood that he wanted Sarah to come off study and proceed to a bone marrow transplant. Mr. Pulaski also contends that he was told by Dr. Wood that CHOP had taken a bone marrow transplant off the table for Sarah. Mr. Pulaski asked Dr. Wood, if this is your child would you do chemotherapy or transplant? Dr. Wood responded by stating that his daughter does not have leukemia but the attendings at CHOP would do chemotherapy. Nonetheless, Sarah was not a candidate for transplant.

Dr. Rheingold and Dr. Wood met the standard of care in discussing with the parents the appropriate conditions for consideration of a transplant, specifically induction failure, positive MRD at the end of consolidation, and a 2nd remission following relapse. Sarah Pulaski did not have any of these clinical presentations, and therefore a consultation with the BMT team was not within the standard of care.

Unfortunately, Sarah Pulaski died as a result of her T-cell ALL and not due the care and treatment provided by the physicians caring for her.

David Alex Jacobsohn, MD, ScM

Chief, Division of Blood and Marrow Transplantation

Children's National Health System

15582932v.1

Case ID: 130802504
Control No.: 15082046