EDITORIAL

RESPONSE TO LETTER BY PULSIPHER *ET AL*

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This Editorial is addressed to the letter by Pulsipher *et al* published in this issue of Leukemia [1].

Thank you for the letter. It is reminiscent of discussions at the Pediatric Oncology Group (POG) meetings in the 1980's. Members engaged in hematopoietic stem cell transplantation for acute leukemia (HSCT) were unable to agree on patient selection and standard regimens of chemotherapy, myeloablation and transplantation; they refused to conduct randomized comparisons. The predictable consequence is that over 20 years later the American Society of Blood and Bone Marrow Transplantation, the editorial and the letter agree that "well-designed randomized controlled trials of HSCT versus chemotherapy have not been conducted successfully", in the letter's words. Without such trials no one can be certain about their relative efficacy and safety, only that HSCT generally requires considerably more procedural risk and investment of human and material medical resources. An irony is that federally sponsored cooperative clinical cancer therapy groups were initiated in the 1950's in order to conduct conclusive clinical trials of cancer treatments.

The editorial pertained only to allogeneic hematopoietic cell transplantation (allo-HCT) but to accommodate the letter its term HSCT will be used.

Several statements in the letter need to be clarified. For example, the statement that "the vast majority of children live happy productive lives, with good health, and normal growth and development" is not substantiated by any data. In this regard, Baker *et al* [2] reported recently that hematopoietic transplant survivors are 3.5 fold more likely to develop severe or life threatening conditions than age and gender matched siblings. Two-thirds had at least one chronic condition and one-sixth a severe or life threatening condition. They also had a 14-fold increased risk of difficulty in holding a job. This confirms earlier reports of long term consequences of HSCT cited in the editorial.

Another example is the citation of Goldsby *et al* [3] regarding late neurological effects of childhood leukemia therapy. The article confirms the

role of cranial radiation as in the editorial but does not report analysis for a possible HSCT effect.

A criticism is raised in the letter that the editorial fails to mention late effects of chemotherapy alone. But two references are made, both demonstrating the low incidence of long term morbidity when preventive radiation became excluded in the 1980's as compared to earlier patient cohorts when it was almost routine, especially when use of anthracyclines and alkylating agents is minimal and synchronous administration of intravenous and intrathecal methotrexate avoided.

The letter is critical of the UKALL R1 and the COG CCG-1952 studies cited in the editorial and suggests that the COG-IBMTR study that is also cited and the ALL-BFM 90 and 95 study of T cell ALL that is not mentioned are better examples of HSCT evaluation. The letter is correct that the COG-IBMTR study does report overall survival but it also states that "because ours is not a randomized study there are several potential biases that may have affected the outcomes described in this report". It also fails to describe and compare early and delayed toxicity of chemotherapy alone vs. chemotherapy followed by HSCT, a necessary component of evaluation. The same is true for the non-randomized ALL-BFM study of T cell ALL which also describes biases of "unknown size and direction" and omits treatment sequelae [4].

Especially disappointing is Table 1 in the letter, citing current COG indications for HSCT [1]. It includes acute lymphoblastic leukemia (ALL) with t (9;22) genotype or hypodiploidy despite COG's recent publications suggesting no advantage of HSCT for these subtypes of ALL.

When treatment of children with acute leukemia changed from palliation to intent to cure in 1962 three goals were set: permanent elimination of leukemia, normal health and capacity for growth, and accessibility to all children in need. Innovative pilot studies of combination chemotherapy followed by science-based comparative trials have achieved the first goal in the majority of children. Treatment modifications such as omitting irradiation and restricting use of alkylating agents, anthracyclines and epipodophyllotoxins have addressed the second goal with considerable

although not complete success. Accomplishment of the third goal is in progress as childhood cancer centers in more privileged nations work with pediatric services in the less privileged to devise simpler, less costly and more readily accessible treatment suited to their circumstances.

The success of HSCT in eliminating residual leukemia depends on producing an alloimmune state in which the donor immune system controls the leukemia by a graft versus leukemia reaction, so far inseparable from a graft versus host reaction. This was first demonstrated in experimental mice by Barnes and Loutit [5] and confirmed in humans with T cell depleted HSCT experiments. This alloimmune state combined with the usual myeloablative regimens, especially total body irradiation, result in lasting growth disturbance, high risk of alloimmune disease, second cancers and early mortality, as described in the editorial and the reference cited above. For this reason HSCT does not and by its very nature will not fulfill the second goal.

With regard to the third goal, there is no realistic possibility that HSCT can ever meet this because of its high consumption of costly human and material health resources in this nation and a world so deficient in them, as reflected in the maternal and child health statistics of this nation and the millions of deaths of mothers, infants and children globally that could be easily prevented or successfully treated by simple low cost measures.

Twenty-five years ago it became apparent that treatment of childhood acute leukemias needed to be targeted to their genetic disorders [6]. The ”sledge hammer”, hazardous, resource-consuming non-specific measures such as combination chemotherapy, radiation and HSCT must be replaced by specific gene targeted approaches. Two highly effective and minimally toxic gene targeted treatments, tretinoin for acute promyelocytic leukemia and imatinib mesylate for Ph positive chronic myelocytic leukemia and ALL, were developed in the late 1980’s and early 1990’s [6,7]. Now in general use, they demonstrate the value of this approach. However, basic and clinical research for other agents targeted to specific genetic aberrations in leukemia has been slow to develop.

The data of the Children's Cancer Group concerning survival of children with ALL published by Nguyen *et al* [9] included nearly 10,000 patients treated over 20 years [8]. They show no significant improvement in 5 year event-free survival of children treated for ALL over this period. It is time for diversion of federal and private research funds from large expensive studies of relatively minute details of "sledge hammer therapy" and flawed comparisons that have not yielded significant improvement in cure rates in recent years to basic laboratory and clinical research to identify specific gene targeted agents that are not only effective but safer and more likely to be accessible to all children. Just as we used tuberculosis chemotherapy as our model for curative chemotherapy of childhood acute leukemia in the 1960's, so it might also be a successful model for accessibility in the next decade.

In composing this response as in the editorial the author was kindly advised by Professors Pui, Gaynon and Simone.

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