Pediatr Blood Cancer 2011;57:908–909

HIGHLIGHT

by Amy Louise Billett, MD[1,2,3]* and Gregory H. Reaman, MD[4]

What Price Cure?

During the past 5 decades, childhood acute lymphoblastic leukemia (ALL) has been transformed from a nearly uniformly fatal disease to one where cure is a reality for most afflicted children [1,2]. Early successful induction regimens treated all children alike with three to four different drugs. Central nervous system directed therapy was proven essential and has evolved over time. Improvements in supportive care such as blood and platelet transfusions, management of fever and neutropenia, and prophylaxis for opportunistic infections has also contributed to this success story. Although the vast majority of the chemotherapy agents used for childhood ALL have been available since the 1970s, treatment has changed in many ways. In addition to induction, all regimens include maintenance chemotherapy, central nervous system directed therapy, and many regimens include delayed intensification. A myriad of prognostic factors, both clinical and biological, are used to risk-stratify therapy. With increasing success in treatment for ALL as well as other childhood cancers, late effects of treatment became an area of increasing of concern and research starting in the 1990s. The ''day one'' talk now routinely includes not only a discussion of the disease and treatment but also the potential long-term effects of curative treatment. Most current clinical trials in pediatric oncology attempt to maximize the therapeutic index of treatment. How can we cure the most patients with the least acute and late toxicity for all? Therefore, ''What price cure?'' is an important question often considered in the field of pediatric oncology.

The article by van Litsenburg et al. in this issue of *Pediatric Blood & Cancer* asks this question in a very new way. What is the literal price of cure in monetary terms? The costs of care were determined for 50 children with ALL treated at a single center on 2 consecutive front-line ALL treatment protocols. ALL9 (1997–2004) stratified patients into two treatment groups based on the presence of commonly used high risk clinical criteria at presentation as well as specific, limited cytogenetic criteria. ALL10 (2004–present) stratified patients into three risk groups (standard, medium, and high) based on common clinical criteria at presentation, prednisone response, more cytogenetic criteria, and minimal residual disease. Compared to ALL9, ALL10 treatment included more chemotherapy agents, including pegasparaginase. Costs of care were determined for all patients. The high risk patients on ALL10 were excluded from the analysis because treatment included stem cell transplantation. Actual (ALL9) or projected (ALL10) event-free survival (EFS) rates were used to calculate outcomes. Patients who relapsed were treated as if deceased. The methodology used by the authors excluded, therefore, the costs associated with salvage therapy at the time of relapse, whether successful or not. The real financial costs of cure might be more accurately assessed using OS rather than EFS in the analysis. The authors found that the total costs of care per patient were almost $50,000 higher in ALL10 than ALL9. Since the projected EFS for ALL10 was higher (standard risk 96%, medium risk 85%) than the measured EFS for ALL9 (non-high risk 84%, high risk 72%), it is projected that the more recent study will result in more life-years saved. The calculated costs per life-year saved were higher for ALL10 for all life expectancies assumed. The authors conclude that new technology (measurement of minimal residual disease) and more expensive medication (PEG-asparaginase) were the major contributors to the increased costs.

As the costs of health care rise and resources become increasingly constrained, we must all consider what we can do to minimize unnecessary costs. Thus, these authors deserve kudos for attempting to analyze cost of treatment for childhood ALL. Although pegasparaginase is more expensive than native *E. coli* asparaginase, we should look at what else could be contributing to the medication costs. In ALL9, all patients received *E. coli* asparaginase 4 times in non-high risk treatment and 13 times in high risk treatment. In ALL10, *E. coli* asparaginase was given eight times in both risk groups. In addition, pegasparaginase was given once in standard risk and 15 times in medium risk treatment. Thus, perhaps the improvement in outcome was not only attributable to the addition of a new ''expensive'' drug, but also to more exposure to asparaginase resulting in longer periods of asparagine depletion. If so, the increased costs per life year saved in ALL10 would be lower if native *E. coli* asparaginase had been given. Even if the improved outcome was directly attributable to increased efficacy of pegasparaginase, perhaps drugs costs are not the only measure that is important. Pegasparaginase is administered every 2 weeks in front line ALL regimens. In contrast, native *E. coli* asparaginase is given three times weekly in some regimens and weekly in others. More clinic visits increases the economic burden on the family in terms of income lost as well as increased costs of transportation, food, or possible day care for other children.

[1]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [2]Division of Hematology/Oncology, Department of Medicine, Children's Hospital Boston, Boston, Massachusetts; [3]Department of Pediatrics, Harvard Medical School, Boston, MA; [4]Office of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland

*Correspondence to: Amy Louise Billett, MD, Department of Pediatric Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. E-mail: amy_billett@dfci.harvard.edu

Received 13 July 2011; Accepted 13 July 2011

DOI 10.1002/pbc.23302
Published online 16 August 2011 in Wiley Online Library (wileyonlinelibrary.com).

The most important question this article raises, however, does not relate to how the cost analysis was done but whether or not cost per life year saved and cost effectiveness should truly be our target in pediatric oncology? Do these authors truly deserve our kudos?

The literature is replete with many analyses of costs in adult health care. A common end point is looking at costs per life year saved. Society generally places a high value on the health and well-being of children. In part, this reflects general culture. There is an economic aspect to this as well. Children who become healthy adults will make future economic contributions to society and will also contribute new members to society when they become parents themselves. Is cost per life year saved an appropriate measure in pediatric oncology? If more patients are cured, they can be expected to make many more contributions, especially if risk-adjusted therapy paradigms continue to attempt to mitigate risk of developing life-altering late effects.

The authors also attribute the increased costs per life year saved in ALL10 to ''the use of new technology'' referring to the use of minimal residual disease testing. We know that costs of technology tend to go down over time and thus the costs of MRD testing are likely to be lower in ''ALL11'' and the increased costs per life year saved may also be lower. Although not stated, we can presume the authors consider flow cytometry, cytogenetics, FISH, and PCR to be standard technology since those were in use for both protocols. Yet, for each of these tests, there was a period of time when the test was new, the technology not widely available, and therefore expensive.

Much of the progress in childhood ALL over the past 20 years has been attributable to better risk stratification and thus better assignment of treatment intensity. Failure to utilize these tests due to increased costs of testing would have prevented progress. Prior to knowing the adverse prognostic significance of Philadelphia-chromosome positive ALL, such patients were treated on standard regimens and had a dismal outcome. With routine use of both cytogenetics and FISH, children with Ph+ ALL are fully identified and are now offered appropriate therapy with the potential for cure without the expense and toxicity associated with stem cell transplantation [3]. Without routine use of cytogenetics, we could not identify children with very favorable prognosis ALL who would otherwise be over-treated and at risk of more late effects and, perhaps, more life-time health care costs [4].

How do pediatric oncologists want to answer the question ''what price cure'' in the future? The EFS and OS rates in childhood ALL used to rise substantially and steadily with each decade. More recently, the increases in rates have been more subtle understandably since excellent outcomes are achieved for so many patients. Continued progress will require still more risk stratification to identify very good risk patients who qualify for reduction of therapy. New technology will always be critical to identify poor risk patients whose leukemia may be appropriate for targeted and, possibly, more expensive therapy. However, if the promise of targeted therapy rings true and successful outcomes can be achieved with less acute and long-term toxicities, then how does one actually calculate expense? For the future, the only appropriate answer to the question ''what price cure'' is obvious. We should not focus on dollars but on how to achieve the optimal balance between treatment efficacy and intensity and late effects of treatment.

REFERENCES

1. Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 2006;354:166–178.
2. Silverman LB, Stevenson KE, O'Brien JE, et al. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985–2000). Leukemia 2010;24: 320–334.
3. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: A Children's Oncology Group study. J Clin Oncol 2009; 27:5175–5181.
4. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: A Children's Oncology Group study. Blood 2008;111:5477–5485.