Cure trends in acute lymphoblastic leukemia: is it time for a revised concept of cure?

Christian Michel Zwaan[1] and Richard Sposto[2]

[1]Dept. of Pediatric Oncology, Erasmus MC/Sophia Children's Hospital, Rotterdam, the Netherlands; and [2]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.

E-mail: c.m.zwaan@erasmusmc.nl *doi:10.3324/haematol.2013.084269*

In this issue of Haematologica, Gatta *et al.* describe cure trends for children and adolescents with acute lymphoblastic leukemia (ALL) who were diagnosed between 1982 and 2002, analyzing data obtained from various cancer registries across Europe.[1] The good news is that the projected proportion of cured children increased significantly over the study period, especially in children in the good prognosis age groups: from 70% to 90% in 1-4 year olds, and from 63% to 86% in 5-9 year olds. The projected outcome data for children below the age of one year and for older children/young adolescents was less satisfactory with increases from 26 to 58% for infants, 52% to 77% for 10-14 year olds, and 44% to 50% for 15-24 year olds. The 'proportion cured' rates are lower than the 5-year survival rates, which is caused by deaths during later follow up, including those due to late disease recurrence, second malignant neoplasms and other toxicities. This is well recognized in prior studies, for instance, from the Childhood Cancer Survivor Study, showing that 66% of deaths in 5-year survivors of ALL were due to relapsed disease or second primary leukemias.[2]

Analysis of cancer outcome data using cure models has a long history[3] and has been used in the past in pediatric cancer.[4] The concept of cure as applied in these models is not always well defined, however. The mixture model of the type used by Gatta *et al.* divides patients into 2 groups, those who are 'cured' and have mortality identical to the normal population, and those who are 'not cured' who have a fixed level of excess mortality.[3] This implies that one can classify individual patients as belonging to one of these 2 groups. In reality, patients who have survived cancer in the short term comprise a spectrum of patients ranging from those with mortality negligibly in excess of normal to those with mortality much in excess of normal. When follow up is limited and a clear plateau in cancer-related mortality has not yet been achieved, the estimates of the 'cured proportion' are really projections, i.e. extrapolations past the data[5] that depend on the linearity and proportionality of risk assumptions implicit in the statistical model. Nevertheless, this model can appropriately reflect the excess mortality among pediatric ALL survivors, and the 'proportion cured' is a useful index of this excess mortality.

In pediatric ALL, progress has come from both reduction in relapse risk as well as treatment-related mortality as competing risks. The relapse rate was reduced as the result of multiple successive therapy-optimization studies carried out by the various collaborative study groups, aiming at optimal risk-group stratification and fine-tuning of existing chemotherapy. Risk-group stratification changed over this time period from host and disease specific parameters established at initial diagnosis (e.g. the NCI-criteria, immunophenotype, prednisone response) to stratification based on minimal residual disease reflecting response to treatment.[6] This allowed for risk-stratified therapy, mainly focused on avoiding undertreatment of relatively resistant cases. Concerning improvements in chemotherapy, important progress was made by using analogs of existing drugs, e.g. using dexamethasone instead of prednisolone,[7] and less so by the introduction of novel agents. More recently, therapy optimization focusses on asparaginase, including asparaginase dose intensification, therapeutic drug monitoring, and the use of novel pegylated formulations, as reviewed by Pieters *et al.*[8] The progress made with these changes are not yet visible in the results reported by Gatta *et al.* as these developments are too recent. At least as important are the improvements in supportive care reducing the number of patients dying from treatment-related mortality,[9] including developments in blood-banking, antibiotics and antifungals, parenteral nutrition and tumor lysis prevention.

When discussing cure, it is important to be precise about what this means. One can say that a patient is cured if the original neoplasm is eradicated, as demonstrated by follow up long past the time of risk of recurrence. In ALL this is nowadays achieved in a large fraction of patients. This definition, however, disregards any residual impact on the patient. Perhaps one should say instead that a patient is cured only if the original neoplasm is eradicated *and* there are no residual sequelae attributable to having had the disease or being treated for it. Very few pediatric cancer patients are cured in this sense. The mixture cure model method used in this paper invokes a definition of cure somewhere in between, but the definition is unavoidably incomplete because the quality of life of surviving patients is not considered. In ALL, at present, we do not have enough knowledge about the exact frequency and impact of these long-term serious toxicities, including for instance cardiomyopathy, neurological sequelae, osteonecrosis, pancreatitis, infertility or second malignancies.[2,10] For newly diagnosed children with ALL in the good prognosis subgroups, the biggest efforts should focus on reducing long-term adverse events whilst maintaining cure, for instance by replacing toxic therapy-elements with less toxic alternatives. However, for the moment, such alternatives are not readily available. Another option is to reduce chemotherapy in patients predicted to have excellent outcome, for instance by low minimal residual disease levels at the end of induction.[11] In patients with Philadelphia-chromosome positive ALL, the addition of tyrosine kinase inhibitors (TKIs) may reduce the number of patients in need of stem cell transplantation, thereby reducing long-term side effects, although the long-term safety profile of TKIs when used in children still needs to be established.[12] Clearly, in order to describe outcome in terms of a revised concept of cure, cancer registries will need to capture data on long-term toxicity in patients in whom the malignancy has been successfully eradicated.

Unfortunately, the cancer registries to date do not capture data on immunophenotype nor on the genetic abnormalities in the leukemic cells, and hence these data could not be analyzed by Gatta *et al.*[1] We feel that such data should be obtained in the future, as genotype-specific therapies are emerging, such as the aforementioned use of TKIs, and hence it becomes clinically important to follow cure trends by genotype rather than the classical features such as age.

Concerning the age groups running behind in projected cure, several remarks can be made. For infants, a first step in improving their outcome has been obtained by implementing a global protocol, recognizing their different sensitivity to chemotherapy.[13] As infants mainly suffer from *MLL*-rearranged ALL, current efforts are directed at developing targeted therapy, for instance by inhibiting the histone methyltransferase DOT1L, which is recruited by chromosomal translocations involving the *MLL*-gene.[14] A first-in-man clinical trial with a DOT1L inhibitor, EPZ-

5676, is currently being conducted (*clinicaltrials.gov identifier NCT01684150*). Regarding adolescents and young adults, many different study groups, including the Dutch, French, United Kingdom and North American study groups, published reports on the superior outcome when using pediatric *versus* adult protocols in this age group, as reviewed by Stock[15] and by Pieters *et al.*[16] Part of the problem may be the increased toxicity that emerges with aging, for instance diminished tolerance when using intensive asparaginase or dexamethasone-based treatment.[15] Another important issue is the heterogeneity in genetic background between pediatric and adult ALL, with a reduced number of good risk and an increased number of poor risk genetic abnormalities. This again stresses the need to capture genotype in the registry database as well as cause of death to determine the relationship between age, genotype and type of event.

Gatta *et al.* analyzed regional variations in projected outcome, and showed that these differences have narrowed over time.[1] In some subgroups, patient numbers were very low, especially when assessing regional variations for infants and older children, questioning the reliability of these results. Access to treatment and potentially ethnic variation may be important contributors to these regional variations. Equal access to therapy for children with cancer is one of the key aims in the FP-7 funded ENCCA project (*www.encca.eu*).[17] Ethnic variations may be relevant and due to polymorphisms influencing drug metabolism. Evidence for this also was provided in pediatric acute myeloid leukemia where outcome differences were seen between patients with various ethnic backgrounds treated on a Children's Oncology Group study.[18] Access to therapy and compliance issues were ruled out as confounders as patients were hospitalized for treatment.

Further progress in ALL should come from understanding the biology of the disease, which may lead to the identification of new treatment targets.[19] However, the recent identification of two novel abnormalities underlying poor risk disease in pediatric ALL, i.e. *IKZF1*-deletions and a '*BCR-ABL* like' gene expression signature, do not directly provide druggable targets.[19,20]

In conclusion, projected cure rates in ALL have improved significantly over time. Since the vast majority of children with ALL are nowadays cured, it is time to re-consider the concept of 'cure' for these patients and to take the long-term adverse effects into account when assessing cure. Improved collaboration between pediatric and adult hematologists is essential for those patients who happen to be diagnosed with ALL as adolescents/young adults. Progress for poor risk subgroups should come from clarifying the underlying biology, which may provide new treatment targets. This also implies that cancer registries for ALL should capture genotype-specific and long-term adverse event data in order to follow cure trends for these patients over the next decade.

Michael Zwaan is Associate Professor of Pediatric Oncology at the Erasmus MC/Sophia Children's Hospital, Rotterdam, The Netherlands. His main area of interest is clinical research, with a focus on early clinical trials in pediatric oncology. Richard Sposto is Director of Biostatistics and Bioinformatics at the Children's Center for Cancer and Blood Diseases, Los Angeles, and Professor of Research, Preventive Medicine and Pediatrics at the Keck School of Medicine, University of Southern California, USA. His main field of interest is biostatistics, with primary focus on its application to clinical and translational research in pediatric hematology/oncology and women's cancer.

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References

1. Gatta G, Rossi S, Foschi R, Trama A, Marcos-Gragera R, Pastore G, et al. Survival and cure trends for European children, adolescents and young adults diagnosed with acute lymphoblastic leukemia from 1982 to 2002. Haematologica. 2013 Feb 12. [Epub ahead of print]
2. Robison LL. Late effects of acute lymphoblastic leukemia therapy in patients diagnosed at 0-20 years of age. Hematology Am Soc Hematol Educ Program. 2011;2011:238-42.
3. Berkson J, Gage RP. Survival curves for cancer patients following treatment. JASA. 1952;47:501-15.
4. Weston CL, Douglas C, Craft AW, Lewis IJ, Machin D. Establishing long-term survival and cure in young patients with Ewing's sarcoma. Br J Cancer. 2004;91(2):225-32.
5. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics. 2007;8(3):576-94.
6. Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grumayer R, Moricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115(16):3206-14.
7. Veerman AJ, Kamps WA, van den Berg H, van den Berg E, Bokkerink JP, Bruin MC, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). Lancet Oncol. 2009;10(10):957-66.
8. Pieters R, Hunger SP, Boos J, Rizzari C, Silverman L, Baruchel A, et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. Cancer. 2011;117(2):238-49.
9. Slats AM, Egeler RM, van der Does-van den Berg A, Korbijn C, Hählen K, Kamps WA, et al. Causes of death - other than progressive leukemia - in childhood acute lymphoblastic (ALL) and myeloid leukemia (AML): the Dutch Childhood Oncology Group experience Leukemia. 2005;19(4):537-44.
10. Nachman JB. Osteonecrosis in childhood ALL. Blood. 2011;117(8): 2298-9.
11. Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2013;14(3):199-209.
12. Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, 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(31):5175-81.
13. Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet. 2007;370(9583):240-50.
14. Bernt KM, Zhu N, Sinha AU, Vempati S, Faber J, Krivtsov AV, et al. MLL-rearranged leukemia is dependent on aberrant H3K79 methylation by DOT1L. Cancer Cell. 2011;20(1):66-78.
15. Stock W. Adolescents and young adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:21-9.
16. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2010;24(1):1-18.
17. Sullivan R, Kowalczyk JR, Agarwal B, Ladenstein R, Fitzgerald E, Barr R, et al. New policies to address the global burden of childhood cancers. Lancet Oncol. 2013;14(3):e125-35.
18. Aplenc R, Alonzo TA, Gerbing RB, Smith FO, Meshinchi S, Ross JA, et al. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2006;108(1):74-80.
19. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012;120(6):1165-74.
20. Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol. 2009;10(2):125-34.