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Position paper/statement by members of the Ponte di Legno group on the right of children to have full access to essential treatment for acute lymphoblastic leukemia

Improved outcome of childhood acute lymphoblastic leukemia (ALL), the most common cancer in children, is one of the great success stories in modern medicine. The approach taken to dramatically improve the cure rate involved the combination of clinical and basic research, mostly conducted with public funds, and intensive collaboration of cooperative groups. As a result, the cure rate has improved from 3% in the 1960s to 80% currently in resource rich countries. We believe that this improved possibility of survival should be considered among a fundamental right of affected children. Providing access to the necessary diagnostic and therapeutic resources for children afflicted with leukemia should be a priority for those who play a role in the relevant areas of medicine and health.

The physicians, clinical investigators, and basic scientists who have signed this statement have been responsible for transforming ALL into a model disease for which there is hope of cure when optimal treatment is accessible. These professionals are fully aware that their successes have also widened the gap of inequality between children living in the resource-rich countries and those living in low-income countries (LICs). Most children live in LICs; hence, most patients with ALL reside in these countries and therefore are subjected to an increased risk of possibly avoidable death.

As citizens, doctors, and researchers, we feel an urgent priority to correct this inequality in ALL treatment. The following is a summary of short- and medium-term plans in this regard:

(i) The first and most rapidly achievable goal is the recognition by international agencies and by concerned

regulatory authorities that the treatment protocols and guidelines developed for children with ALL are essential. In this regard, antileukemic drugs used in these protocols should be qualified as *essential* drugs.

(ii) Centers or groups of excellence should be developed in LICs. Our experience in various LICs has shown that the efficacy and safety of chemotherapy can be ensured in centers and by groups who are trained and motivated to adopt policies of high-quality ALL care, which include the use of well-designed protocols.

(iii) On the basis of concepts and strategies developed for use in other disease areas (from tuberculosis to AIDS), we recommend broadening the scope of the *essential drugs list* and documenting not only the selection and use of drugs but also the implementation of the treatment strategy.

(iv) Within a framework in which the fundamental rights of children are the reference value, we commit our groups to strongly support all activities toward this goal; but we request the recognition by WHO and other concerned national and international agencies that the care of children with ALL (as well as with other curable cancers) is deemed essential.

(v) We advocate a price policy for drugs used in the protocols; the purpose of the policy will be to diminish the treatment barrier of high drug costs substantially; we recommend that the national authorities support the centers where staff are committed to *essential protocols* and that national authorities document compliance with these protocols.

We are only too aware that the resource allocation for ALL does not currently coincide with public health priorities in many countries. However, we are convinced – and supported by our experience – that ALL is a model for all curable cancers; expanding efforts in treatment of ALL in LIC will result in the mobilization of important new energies, stimulation of imaginative solutions, enrichment of motivations, and broadening of public awareness. We emphasize that a policy of drastic cost-cutting in ALL treatment is feasible for two main reasons (besides and beyond any ethical consideration): (i): the market implications are minimal, because the size of the patient population is relatively small; and (ii) there will be no risk of misdirection or mismanagement of drugs as they become available, because their use will be accounted for by centers of expertise who are committed to documenting compliance through registration of all patients enrolled on treatment protocols.

All subscribers to this memorandum, representing the majority of the Childhood Leukemia Treatment Consortia, herewith emphasize the right of all children in the world to full access to the essential treatment of ALL and other cancers, and call upon all authorities concerned to recognize and support all measures that

can promote this right to a *chance of cure*. This statement was approved in principle by the following representatives of these study groups in San Diego in December 2003:

- Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP): M Arico, G Basso, A Biondi, V Conter, G Masera, G Tognoni, MG Valsecchi
- Berlin-Frankfurt-Münster Group (BFM): G Cario, H Gadner, O Haas, J Harbott, R Panzer, H Riehm, M Schrappe, A Stackelberg, M Stanulla, M Zimmermann
- Children's Oncology Group (COG): B Camitta, W Carroll, P Gaynon, S Hunger, J Nachman, K Schultz, N Winick
- Cooperative Study Group for Childhood Acute Lymphoblastic Leukemia (COALL): M Horstmann, G Janaka-Schaub
- Czech Pediatric Hematology (CPH): J Stary, J Trka
- Dana-Farber Cancer Institute (DFCI) ALL Consortium: S Sallan, L Silverman
- Dutch Childhood Oncology Group (DCOG): R Pieters, A Veerman
- European Organization for Research and Treatment of Cancer-Childhood Leukemia Group (EORTC-CLG): Y Bertrand, S Suciu
- French Acute Lymphoblastic Leukemia Study Group (FRALLE): G Leverger
- Japan Association of Childhood Leukemia Study (JACLS): K Horibe
- NCRI/Medical Research Council Childhood Working Party, United Kingdom Acute Lymphoblastic Leukemia (MRC-UKALL): OB Eden, C Harrison, B Gibson
- Nordic Society of Pediatric Haematology and Oncology (NOPHO): E Forestier, K Schmiegelow, K Vetteranta
- St. Jude Children's Research Hospital (SJCRH): D Campana, E Couston-Smith, WE Evans, R Handgretinger, C-H Pui, MV Relling
- Taiwan Pediatric Oncology Group (TPOG): D-C Lang
- Tokyo Children's Cancer Study Group (TCCSG): A Manabe, M Tsuchida
- D Pinkel.

Chronic myeloid leukemia-specific T-cell responses

In chronic myeloid leukemia (CML), the chimeric p210 fusion protein resulting from the bcr-abl fusion gene produced by the t(9;22)(q34; q11) translocation, in virtue of the unique sequence of amino acids contained in the junctional regions, which is CML-specific,

furnished the rationale for a peptide vaccine strategy in this disease.¹ Although treatment of CML has been revolutionized by imatinib mesylate (see previous articles in this journal)²⁻¹² a portion of patients are or become resistant to this drug,¹³ so that alternative treatments have been proposed.¹⁴⁻¹⁷ Theoretically, CML-specific T cells might be useful for therapeutic purposes. As discussed by Posthuma and co-workers in this issue,¹⁸ a prerequisite for a CML-specific T-cell response is proteasomal degradation of intracellular BCR/ABL protein resulting in presentation of BCR/ABL-specific oligopeptides by HLA class I or HLA class II molecules on the membrane of leukemic cells and the presence of T-cells with a T-cell receptor (TCR) that can recognize these peptide-HLA complexes. Until now there is no definite proof of the existence of such CML-specific responses *in vivo*. In their work, Posthuma and co-workers¹⁸ show that proteasomal degradation of BCR/ABL protein can generate a CML-specific HLA-A*0301 restricted peptide, but high-avidity T-cells recognizing this BCR/ABL-specific antigen could not be demonstrated.

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