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Redefining "rare" in paediatric cancers

See **Series** pages e52, e62, and e70

Rare cancers are a diagnostic and therapeutic challenge, particularly in the paediatric population: the total number of paediatric cancer cases accounts for only 1% of all cancers diagnosed in all age groups (figure). Despite its relative rarity and its high chance of cure, paediatric cancer remains the leading cause of death by disease among children in developed countries. In this issue of *The Lancet Oncology*, a Series of three papers[1–3] focuses on how studies can be ameliorated to improve clinical outcomes in adults with rare cancers. The authors of the three reviews all draw attention to the absence of a consensus definition of rare cancer. The European Society of Medical Oncology defines rare cancers as those with an incidence of less than six per 100 000 per year, whereas the US National Cancer Institute defines rare cancers as having an incidence of 15 per 100 000 per year.[4] Rare cancers are estimated to account for 27% of all cancers, or fewer than 40 000 new cases per year in the USA, and cause a quarter of cancer deaths in adults.[1,2]

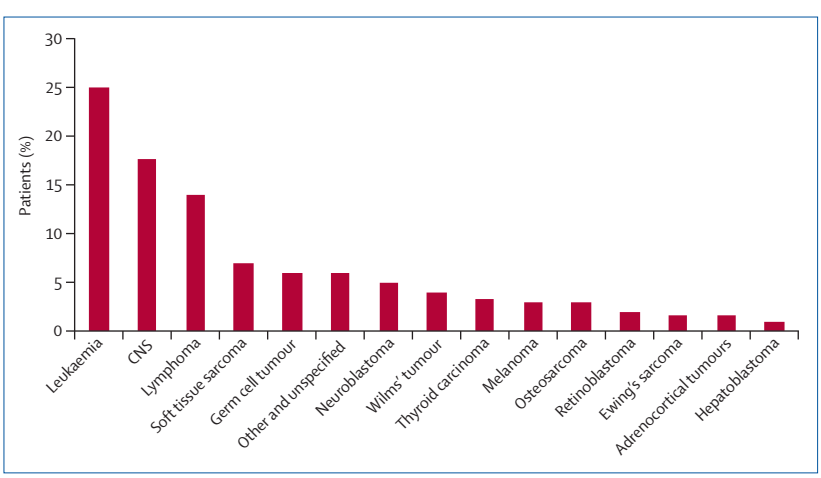

Figure: **Distribution of malignant disease, including rare cancers, in patients younger than 20 years**
Data are from the *International Classification of Diseases for Oncology* by the Surveillance, Epidemiology, and End Results Program and are based on the 2000 US standard population. According to the Children's Oncology Group's definition, rare paediatric cancers include thyroid carcinoma (37%), melanoma (30%), other carcinomas (25%), colorectal carcinoma (5%), nasopharyngeal carcinoma (3%), and adrenocortical carcinoma (1%).

If the adult definition were used, all childhood cancers would be classed as rare. But within the paediatric community, no uniformly accepted definition exists for rare cancers. The European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT) defines rare childhood cancers as those with an incidence of less than two per million that are not being investigated in clinical trials, whereas the Children's Oncology Group has adopted a qualitative definition based on a low prevalence in patients younger than 5 years (except for adrenocortical carcinoma), a higher incidence in adults (including older adolescents and young adults) than in children, and an epithelial (rather than mesenchymal) tumour origin.[5] The Children's Oncology Group definition excludes some rare cancers reported almost exclusively in children, such as pancreatoblastoma and pleuropulmonary blastoma.[5] Irrespective of the definition, rare cancers are estimated to account for roughly 5–10% of all childhood cancers.[5]

In the era of precision medicine, Niki Boyd and colleagues[1] suggest that the definition of rare cancers should also include specific molecular subtypes of common cancers that have prognostic or therapeutic relevance, and provided non-small-cell lung carcinomas as a prime example for adult cancer.

It has long been recognised that each major phenotypic and genotypic type of childhood acute lymphoblastic leukaemia has many subtypes with heterogeneous biological features and treatment responses.[6] For example, in Philadelphia chromosome-like acute lymphoblastic leukaemia, which accounts for roughly 10% of childhood cases, there are subtypes that would respond to *ABL* tyrosine-kinase inhibitors; in others, the JAK–STAT pathway is implicated—a finding that offers novel opportunities for targeted therapeutics.[6] In hypodiploid acute lymphoblastic leukaemia, which accounts for only 2% of childhood acute lymphoblastic

leukaemia, the near-haploid subtype is characterised by genetic alterations targeting receptor tyrosine-kinase signalling and RAS signalling, and the low-hypodiploid subtype by alterations of *RB1* and *TP53* that are often inherited, which expands the range of cancer predisposition syndromes.[7]

Risk-based therapies can also be applied in medulloblastoma, the most common malignant brain tumour in childhood, in which the rarest molecular subtype, which is defined by mutation in the *CTNNB1* gene, has the best treatment outcome (5-year overall survival around 95%), and subgroup 3 medulloblastoma that often has either overexpression or amplification of the *MYC* has the worst (5-year overall survival around 50%).[8] Gastrointestinal stromal tumours in younger patients (median age 20 years) are primarily driven by mutational or epigenetic loss of function in the succinate dehydrogenase complex, explaining a lack of sensitivity to standard adult therapies that target KIT and PDGFR.[5] Furthermore, germline mutations in predisposition genes, which are noted in as many as 8·5% of children and adolescents with cancer, should be included when considering future stratification of, and management strategies for, specific diseases, as this information could directly affect care and genetic counselling of patients and families.[9]

To improve research and the outcome of treatments for rare cancers, Jean-Yves Blay and colleagues[2] provide clear examples of how research networks and consortia can facilitate interaction between academic groups, the pharmaceutical industry, patient advocacy groups, primary care doctors, and health authorities. The European LeukemiaNet, which consists of 194 participating centres in 39 countries, has been very successful in advancing leukaemia-related research and health care in adults. The EXPeRT group provides exemplary expertise in the management of selected paediatric rare solid tumours, and several registries are actively recruiting patients with rare paediatric cancers, including adrenocortical carcinoma and pleuropulmonary blastoma.[5] Since 1995, 15 major national study groups or major institutions worldwide have formed the Ponte di Legno Group, an international working group that focuses on rare and drug-resistant subtypes of acute lymphoblastic leukaemia, and has improved treatment strategies for several of them.[6]

To overcome the problem of insufficient numbers of patients with rare cancers for conventional clinical trials, Lucinda Billingham and coworkers[3] suggest several strategies to maximise recruitment, minimise sample size, and maximise the usefulness of the evidence by using alternative methods of statistical analysis, which could change clinical practice. In recognition of the fact that determination of minimal residual disease is one of the most important prognostic factors for acute lymphoblastic leukaemia, the US Food and Drug Administration is reviewing the use of this biomarker in the assessment of new drugs for haematological malignancies.[10] Expanding on the rapidly growing area of precision medicine, the National Cancer Institute will launch a paediatric Molecular Analysis for Therapy Choice trial that will rely on DNA sequencing to identify therapies that can target genomic tumour abnormalities in children in whom standard therapy was unsuccessful.

In summary, scientific advances together with growing international collaboration and partnerships between the pharmaceutical industry and governmental groups provide unparalleled opportunities to advance the understanding and treatment of rare cancers in adult and paediatric patients.

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We declare no competing interests.

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For the **European LeukemiaNet** see http://www.leukemia-net.org