REVIEW

Childhood cancer survival and future challenges

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The history of childhood cancer treatment is one of the major success stories of the second part of the 20th century, where cure rate improved from no survival in 1950 to more than 70% currently. This is due to the development of dedicated paediatric oncology units, prospective clinical trials, and improved supportive care. Challenges for the 21st century include finding therapies that will cure the other 30% of children and reduce the complications of treatment. Only about 20% of the world's children have access to this type of specialised care and a major focus area is how to ensure improved access to these treatment modalities for the other 80% of the world's children.

Childhood cancer is a rare disease, accounting for less than 1% of all cancers and affecting 1 in 600 children under 15 years of age.[1,2] Currently, more than 70% of these patients are cured with modern treatment modalities that progressively improved from 1950 onwards.[1,3] However, the cure rate for adult cancer is not so good, partly because of the differences in biology. Childhood cancer derives mainly from non-ectodermal embryonal tissue, whereas adult carcinomas derive from epithelial tissue.[2] Childhood tumours are much more responsive to chemotherapy than carcinomas. Furthermore, the improved outcome includes several other factors, such as specialised care for these children in dedicated paediatric oncology units where the necessary expertise is concentrated, as well as the enrolment of patients into well-designed prospective clinical trials.[1,4] These trials are based on a therapeutic empirical basis, and strict adherence to treatment protocols resulted in the improved cure rate.[1,3] Paediatric oncologists also improved the staging of the underlying cancer, ensured good pathology reviews and combined chemotherapy with surgery and radiotherapy. There was also a major improvement in supportive care, which has allowed paediatric oncologists to use potentially lethal therapies in order to achieve cure.

Improved survival of the different childhood cancers, with special attention to ALL

The most common childhood cancer is acute lymphoblastic leukaemia (ALL). The success of childhood ALL treatment during the past 50 years is one of the greatest achievements with regard to cancer treatment.[4] Before 1950 the average survival of a child with ALL was 3 months. The years 1950 - 1962 saw the development of the basics of childhood ALL treatment.[4] Aminopterin was the first drug used, and subsequently either 6-mercaptopurine or prednisone as single drugs – but all patients died.

From 1960 to 1967 combination drug protocols were established, using vincristine, asparaginase, cyclophosphamide, daunorubicin, and cytosar. However, central nervous system (CNS) involvement was a major problem during this period and led to the introduction of early prophylactic treatment in the form of CNS radiation. The early St Jude studies showed a 20% survival. The St Jude Study V, started in 1967, determined the maximum tolerated dose, and introduced improved, aggressive supportive care and CNS prophylaxis, resulting in a 40% disease-free survival.[4]

The period 1970 - 1980 saw the development of different treatment strategies by the following groups: Berlin-Frankfurt-Münster study group (BFM, Germany), Pediatric Oncology Group (POG, USA), Children's Cancer Group (CCG, USA), and Dana-Farber (USA).[3,4] These studies lengthened remission periods, determined some of the prognostic features and improved supportive care. This period was also characterised by studies determining the late effects of cancer treatment. Treatment became successful, with 90% of children achieving initial remission. By 1980 the disease-free survival was 50%.

From 1980 to 2000 treatment protocols increased long-term survival to 75% and deaths in remission were rare. This period saw the development of non-radiation, but chemotherapy-based treatment as standard therapy for CNS prophylaxis, as well as the use of molecular genetics for improved stratification of treatment. Currently, in 2007, the strengths of childhood ALL treatment are the great record of success, the effective clinical trial infrastructures, and the large evolutionary empirical (trial and error) approach. The weaknesses are that there has been no major new treatment agent in 30 years, and that the treatment protocol is complex, expensive and potentially toxic. The care for survivors is also not well developed and the aetiology of leukaemia is largely unknown, resulting in lack of preventive strategies.

Survival has also improved for all other haematological malignancies such as acute non-lymphocytic leukaemia (>50%), Hodgkin's lymphoma (>90%) and non-Hodgkin's lymphoma (>80%).[2,5] The survival of children with solid tumours is not as marked, but survival of those with brain tumours has significantly improved.[2,5] The same holds for embryonal cancers such as nephroblastoma, neuroblastoma, and embryonal rhabdomyosarcoma, with statistically significant survival, but not for retinoblastoma, chondrosarcoma and fibrosarcoma.[2,5] Rare cancers such as melanoma, osteosarcoma and thyroid carcinoma have not yet shown the same improved survival.

Future challenges in paediatric oncology

Currently, the challenge for paediatric oncology is finding curative treatments for the nearly 30% of children who are not cured.[1,4] The period 2000 - 2025 will probably see the development of new treatment agents for childhood cancer and revolutionary approaches with curative, targeted treatment with small molecules (biological factors). There will also be the development of better diagnostic methods for molecular subtypes, using micro-array technology, which, according to Simone, may first create confusion before assisting in improved risk and treatment stratification and improved survival.[4]

It will also be important to find ways of reducing the toxicity and long-term effects of cancer treatment, as well as the current treatment cost.[6] For example, in the case of nephroblastoma, excellent survival rates were maintained, while there was a progressive reduction in therapy, especially radiotherapy, with less skeletal deformities.[1] Further research is needed to decrease treatment intensity in low-risk disease or to develop new protective drugs that can protect target organs against damage by chemotherapy. There is also a need for sophisticated programmes to accommodate the needs of long-term survivors.[6] These are children or young adults who survived their childhood cancer for more than 5 years. These programmes must include the transition of care from the paediatric oncologist to the adult physician, which is very important as certain late effects only manifest in adulthood.[6] The first survivors of childhood cancer are now reaching middle age, with little knowledge of their health care needs or complications due to cancer treatment.[6] Curing a child with ALL is also financially expensive, as reported in the study by Raiahala *et al.*,[7] but as these cured children will have a normal life expectancy, the cost per quality-adjusted life years gained is low.

Prevention is another focus area and therefore the aetiology of the different childhood cancers is being investigated.[1,4] Various reports indicate several possible causative agents. These studies include addressing environmental factors such as exposure to electromagnetic fields, which is associated with increased risk of childhood cancer.[1] More attention is placed on the underlying biology of childhood cancers and 11q23 gene arrangements have been identified as being common in infants with leukaemia.[1] Late effects of cancer treatment include secondary cancers that develop, especially when treated with epipodophyllotoxins.[1] Breastfeeding is associated with a lowered incidence of childhood leukaemia.[1] As more knowledge becomes available, better strategies for prevention can be planned and implemented.

Another concern is that only about 20% of the world's children have access to cancer treatment, while the main killers of children in developing countries are communicable diseases such as diarrhoea and infections.[8,9] However, as these countries address these diseases effectively, cancer will emerge as a major cause of death, as seen in developed countries, where cancer, after accidents, is the leading cause of death in children.[2] The major causes of childhood death in South Africa are HIV/AIDS, followed by low birth weight, diarrhoea and lower respiratory tract infections.[10] The under-5 mortality has in fact increased from 60 per 1 000 live births in 1990 to 95 per 1 000 live births in 2000, mostly owing to the HIV pandemic.[10] Of concern is that the clinical symptoms and signs found in haematological malignancies in children are similar to those in HIV/AIDS and tuberculosis, which may lead to missed or late diagnosis, resulting in death in the case of inaccurate diagnosis.[11] Therefore it is important that the danger signs of childhood cancer are included in the integrated management of childhood illnesses to alert health care workers to have a high index of suspicion when dealing with lymphadenopathy with or without anaemia.[12] These danger signs include the following: pallor, pathological pain (either bone pain or early morning headaches), an unexplained or abnormal mass, persistent unexplained fever, weight loss, lethargy, neurological signs or eye changes. Curing a child with cancer will result in normal life expectancy, which is important in a country such as South Africa that is severely affected by the HIV/AIDS pandemic.

Conclusion

Paediatric oncology as a discipline has changed the outcome for children with cancer – from certain death to a cure rate of more than 70% in the last 40 years. This can serve as an example of how successfully conducted clinical trials can improve outcome. It is also important to focus on further improvement of outcome, probably using biological agents, as well as improved cancer treatment access for children worldwide. In developing countries it is important to train primary health care workers in the early detection of children with potential cancers and to establish functional paediatric oncology units to which these patients can be referred as emergency patients. Currently the International Paediatric Oncology Society (SIOP) supports several programmes in developing countries to improve access of children to cancer treatment.[1] With improved cancer survival in developing countries, there will be an increasing need for long-term support programmes for survivors.

References

1. Craft AW. Childhood cancer – mainly curable so where next? *Acta Paediatr* 2000; 89: 386-392.
2. Gatta G, Capocaccia R, Coleman MP, Ries LAG, Berrino F. Childhood cancer survival in Europe and the United States. *Cancer* 2002; 95: 1767-1772.
3. Simone JV, Lyons J. The evolution of cancer care for children and adults. *J Clin Oncol* 1998; 16: 2904-2905.
4. Simone JV. History of the treatment of childhood ALL: a paradigm for cancer cure. *Best practice and Research Clinical Haematology* 2006; 19: 353-359. http//www.sciencedirect.com (accessed 17 June 2007).
5. Gatta G, Capocaccia R, Stiller C, *et al.* Childhood cancer survival trends in Europe: A EUROCARE working group study. *J Clin Oncol* 2005; 23: 3742-3751.
6. Meadows AT. Pediatric cancer survivorship: research and clinical care. *J Clin Oncol* 2006; 32: 5160-5165.
7. Raiahala J, Rikkonen P, Kekäläinen L, Hekkiö M. The cost analysis of the treatment of acute childhood lymphoblastic leukaemia according to the Nordic protocols. *Acta Paediatr* 2000; 89: 482-487.
8. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet* 2003; 361: 2226-2234.
9. UNICEF. *The State of the World's Children 2006*. New York: UNICEF, 2006.
10. Bradshaw D, Bourne D, Nannan N. *What Are the Leading Causes of Death Among South African Children?* Tygerberg, Cape Town: South African Medical Research Council, 2003. http://www.unicef.org/southafrica/SAF_publications_mrc.pdf (accessed 17 June 2007).
11. Hesseling PB, Hartley P, Zietsman L, van Lill S, Preston-Martin S, Wessels G. Incidence of acute lymphoblastic leukaemia in white and coloured children in the Western Cape. *S Afr Med J* 2004; 94: 533-536.
12. Hartley P, Daubenton JD. Curing cancer in children – early recognition and appropriate treatment are the key. *S Afr Med J* 2001; 91: 40-41.