HK J Paediatr (new series) 1999;**4**:111-117

26th C Elaine Field Lecture

Prospects for the Child with Cancer in the New Millennium

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Abstract In the new millennium, childhood cancer is likely to become more important as a child health problem in countries where infection and malnutrituon assume lesser importance. The remarkable successes achieved over the past 50 years in the treatment of paediatric malignancy have resulted in the cure of most types of childhood cancer. In many cases it is even possible to refine treatment so that therapy in selected early localised tumours with good prognostic features could be reduced without sacrificing excellent results and more intensive treatment reserved for high-risk cancers. This article gives a brief review of the current results of treatment of the spectrum of childhood cancers. Efforts at refinements of treatment are pointed out. Long-term effects of therapy relating to major organ systems as well as risks of second cancers and the psychological cost of cure are briefly discussed. Future challenges are posed for the new millennium to achieve the ultimate goal of cure which is a full restoration of normal health, not just an elimination of disease.

Key words Childhood Cancer; Treatment; Cure

In the new millennium, childhood cancer is likely to become more important as a child health problem from at least two aspects. Firstly, as the problems of infection and malnutrition become less important, particularly in developing countries, paediatric malignancy is likely to emerge as a major cause of morbidity and mortality. Already in developed countries, cancer is, after accidents, the second commonest cause of death in children beyond infancy. It has been estimated by the WHO that every year worldwide about 200,000 children below the age of 15 years receive the diagnosis of cancer and most of these cases (estimated by WHO to be about four-fifths) occur in less developed countries.[1,2] The commonest childhood cancer is leukaemia, accounting for about 35-45% of cases, the rest are solid tumours. Secondly, most forms of cancer in children are now curable. [3] In the relatively short 50 years since Dr. Sidney Farber reported the transient effect of aminopterin on leukaemia, there has been really remarkable successes in the treatment of childhood cancer. In the USA, the Statistics, Epidemiology and End-Results (SEER) registries have reported an overall cure rate of about 80%.[2] By the Year 2000, it is estimated that one in every 1000 young adults between 20 and 45 years of age in the USA is a childhood cancer survivor. Many factors are responsible for this wonderful achievement. The most important is the successful application of multimodal therapy namely radiotherapy, surgery and especially the increasingly dominant role of chemotherapy. No less vital is the better standard of supportive care and management of infections. Clinical research collaboration is also critical as many advances in treatment would not have been achieved if not because of the successful implementation of international multicentre cooperative trials.

However, cancer in children is a very heterogeneous disease, even within a cancer type and the prognosis could vary considerably within its subsets. In this lecture, I wish to briefly survey the field of paediatric malignancy to see whether each type of cancer satisfies the criteria of biological cure [4] which are: 1. completion of all cancer treatment; 2. continuous freedom from clinical and laboratory evidence of cancer; 3. minimal or no risk of relapse as measured by the plateau of cancer-free survival. However a real cure, as opposed to mere freedom from disease, would mean a return to normal health, free of the long-term effects of treatment.

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Received April 28, 1999

Leukaemia

Current overall long-term event-free survival (EFS) rates of international studies of childhood acute lymphoblastic leukaemia (ALL) range from 62-78%, achieved mainly through the early use of intensive chemotherapy.[5-7] Most of the survivors can be regarded as cured. However, ALL is prognostically very heterogeneous and several risk groups can be recognised prospectively. [5,8] High-risk cases include those with white blood cell (WBC) counts exceeding $50x10^9$/L (more so if $>100x10^9$/L); aged <1 year or >10 years; T-cell immunophenotype; B-cell ALL; translocations t (4;11), t (9;22), t (1;19); slow response to induction therapy and those with extramedullary leukaemia at diagnosis. It is debatable whether 'low-risk' cases can be reliably identified prospectively and given less intensive treatment. It is now recognised that the single most important prognostic factor is the type of treatment given because known adverse prognostic features could be eliminated by the use of intensive therapy. [8] For example results from the German Berlin-Frankfurt Munster (BFM) studies have shown that, with early intensive induction-consolidation therapy, children with high WBC counts, T-ALL or t(1; 19) do as well as those with standard-risk ALL. [7] However, for infants with t (4;11) or those with t (9;22) or patients who are slow to achieve early remission, EFS rates are significantly less despite the use of intensive chemotherapy. [5] Another major problem is the 20-30% of patients who relapse, especially early during treatment. Bone marrow transplantation (BMT) in second complete remission (CR) in those with histocompatible siblings can cure about 40% of such cases. [9] It is still unclear whether BMT when performed in first CR can cure those with t (4; 11) or t (9;22).

The results of chemotherapy for childhood acute myeloid leukaemia (AML) have improved. Success with induction of remission has increased to as high as 80% and for selected "good-prognosis" cases, BMT in first CR is no longer indicated.[10] Overall, with myeloablative induction therapy, long-term survival rates have climbed to about 50%. BMT when performed in 1st CR, gives a cure-rate of 60-70%.[9] In acute promyelocytic leukaemia a permanent remission could be induced with a non-myelosuppressive drug, all-trans-retinoic acid, thus avoiding the need for BMT.[11]

In contrast, childhood chronic myeloid leukaemia (CML), responsible for only about 5% of all childhood leukaemias, cannot be cured by chemotherapy alone. BMT is indicated for all cases, giving a cure rate of 80-90% when done in chronic phase.[9] In the rare event of relapse post-BMT, 60-70% of such cases could be further salvaged with immunotherapy, through the use of donor lymphocytic infusions (DLI).[12]

Brain Tumours

For brain tumours, the second commonest childhood malignancy after leukaemia, surgery and radiotherapy have been largely responsible for the improvement in prognosis. The role of adjuvant chemotherapy is still under investigation but is promising. Fifty to sixty percent of "standard-risk" patients with posterior fossa medulloblastoma (MBL) can be cured by a radical tumuor resection followed by craniospinal irradiation, consisting of 3600 rads to the cranium with a boost of 5500 rads to the posterior fossa and 1200 rads to the spine. Unfortunately, this is associated with significant long-term neuropsychological sequelae especially to the developing brain for the very young. Adding chemotherapy perioperatively has no significant effect on disease-free survival in 'standard-risk' medulloblastoma patients, unlike in high-risk cases (with gross residual tumour ± metastases),[13] but allowing a reduce dose of craniospinal irradiation to be given. For high-grade astrocytomas (anaplastic astrocytoma, and glioblastoma multiforme) the prognosis is poor with median time to progression of less than one year from diagnosis.[14] However, for the minority (<40%) of patients who can achieve a >90% surgical tumour resection, the progression-free survival (PFS) is improved with adjuvant chemotherapy for both anaplastic astrocytoma (42% versus 14% 5 years PFS) and glioblastoma multiforme (27% versus 4%).[14] Children below the age of 3 years presenting with brain tumours not only have a poorer prognosis for each tumour type compared to their older counterparts, but also have a greater propensity to more adverse consequences of radiation therapy. At present under investigation are promising strategies aimed at delaying or omitting radiation by the use of intensive chemotherapy and autologous stem cell rescue (ASCR).[15]

Lymphomas

The increasingly dominant role of chemotherapy in paediatric oncology is best illustrated in childhood non-Hodgkin's Lymphoma (NHL). The use of chemotherapy alone, whether in intensive pulses of short duration as for B-NHL (e.g. abdominal NHL) or for 2 years as for T-cell NHL (treated like in ALL) has produced cure rates as high as 95% (for stage I and II), 85% (for stage III B-NHL, B-ALL) and 75% for T-cell NHL.[16,17] Even for cases of anaplastic large-cell lymphoma (ALCL) the long-term outlook has improved considerably with chemotherapy.

The BFM has reported an EFS at 9 years of 80% for the Ki-1 ALCL using intensive pulses of short duration as chemotherapy.[18]

In paediatric Hodgkin's disease, the use of chemotherapy alone for all stages of the disease has not only cured over 90% of patients but also has obviated the need for staging laparotomy.[19] However, this approach is associated with significant long-term chemotherapy-related complications of sterility in boys and secondary AML. These could now be avoided by reducing the duration and intensity of chemotherapy and by adding low-dose involved-field irradiation.

Wilms' Tumour

The management of Wilms' tumour is a success story in paediatric oncology where the principles of multimodal therapy were first applied. Treatment is based on the stage of the disease and the histology. In this modern age, very few patients with Wilms' Tumour of favourable histology (FH) should die of the disease, as the prognosis even for stage IV is at least 80% (Table 1). It is now not unusual to be able to cure even patients with pulmonary metastases or relapses. In fact, it is now possible to further refine treatment to reduce toxicity without loss of efficacy. Stage I tumours can now be cured with vincristine alone for merely 10 weeks; radiation can be omitted for stage I and II and the dose of tumour bed irradiation in stage III disease can be safely halved to 1000 rads. Even the negative impact of unfavourable histology can now be partly overcome with the use of intensive chemoradiotherapy.[20]

In the National Wilms' Tumour Study (NWTS) III, 4-year relapse-free survival (RFS) rates of 80-90% and 70% have been reported for the 5% of tumours showing anaplasia and the rarer 2.5% of patients with clear cell sarcoma of the kidney respectively.[20] Unfortunately, another 5% of cases with malignant rhabdoid change has only a 23% chance of a 4-year RFS rate despite the use of intensive chemoradiotherapy.[21]

Neuroblastoma

For neuroblastoma (NBL), future comparisons of treatment results will be facilitated by the adoption of the International Neuroblastma Staging System (INSS). There has been little advance in the management of the majority of NBL patients with poor-risk stage 4 disease (about two-thirds) with the long term survival rate remaining at about 10-12%.[22] Non-randomised studies conducted by the Children's Cancer Group (CCG) suggest an advantage of consolidation chemoradiotherapy and autologous BMT over continued chemotherapy for metastatic neuroblastoma.[23] Low-risk Stage 1 and Stage 2A disease (about 10% of patients) can be cured by surgery in 85-90% of cases.[22]

Stage 3 regional disease can still be cured with multimodal therapy but there is evidence that non-stage 4 tumours that do not show N-myc amplification can be treated with surgery alone.[24] Most infants with neuroblastoma can be cured, irrespective of stage but young infants below the age of 6 weeks with stage 4s disease are at high risk of cardiopulmonary collapse due to extreme tumour compression.

Retinoblastoma

Traditionally, a >90% cure rate has been achieved in retinoblastoma (RBL) with the use of enucleation with or without external beam radiation (EBR). However, there is significant morbidity associated with the use of EBR, i.e. cataract, retardation of bone and soft tissue growth, loss of lacrimal function, in addition to a 35% risk of second cancers over a 30-year period. [25] Chemoreduction, the application of chemotherapy to reduce tumour volume to permit less damaging local therapy, e.g. cryotherapy, laser treatment, has ushered in a new era in the treatment of retinoblastoma. It not only saves lives but sight as well. In a study from Toronto on 32 patients with tumours in 46 eyes with unfavourable prognosis that otherwise would

Table 1 NWTS-III (FH)

Stage	Treatment	4y RFS	Survival	Comment
I	V, Act, 11w	89%	95.6%	No RT; ?shortest? Omit Act
II	V, Act, 15m	87.4%	91.1%	No RT, ADR
III	V, Act, ADR, 15m + RT (1000 cGY)	82%	90.9%	No CYC; 1000 cGy = 2000cG
IV	V, Act, ADR 15m ± RT (1000 cGY)	79%	80.9%	No CYC; 1000 cGY = 2000cG

V: Vincristine; Act: actinomycin D; ADR: adriamycin; RT: radiotherapy; CYC: cyclophosphamide; FH: favourable histology

require enucleation or EBR, such chemoreduction using vincristine, VM 26, cisplatinum in association with cyclosporin A to minimise the emergence of drug resistance has resulted in the restoration of stable useful vision in 30 patients (94%) and the cure of retinoblastoma in 37 eyes (80%).[26]

Malignant Germ-Cell Tumours (MGCT)

This is a heterogeneous group histologically divisible under the WHO Classification, into: 1. Dysgerminoma (Seminoma), and 2. The Non-Seminomatous Germ-Cell Tumour (nSGCT) group encompassing endodermal sinus tumour, choriocarcinoma, immature teratoma, embryonal carcinoma and a mixed group. In children, it occurs more commonly in the gonads (testis or ovary) and the sacrococcygeal region and less commonly in the brain, vagina, mediastinum, retroperitoneum and the liver. An important advances is the use of biological markers, e.g. alpha foetoprotein (αFP) or βHCG not only in diagnosis but also in follow up. Where tissue diagnosis is difficult, e.g. in the pineal region, an elevated αFP level with demonstration of tumour by computer tomography (CT) or magnetic resonance imaging (MRI) techniques is acceptable for purposes of diagnosis and management. Chemotherapy has emerged to play a dominant role in management, sometimes reducing and even replacing the part played by radiotherapy and surgery. As in other childhood solid tumours, staging is important. Stage 1 testicular tumours may be treated with surgery alone but close follow up with αFP levels is mandatory to detect the 20% possibility of relapse. In partially resected or unresected disease, chemotherapy using five to seven courses of bleomycin, etoposide and cisplatinum (BEP) over several months results in a cure in the majority of (70-80%) cases.[27,28] The role of radiotherapy for this disease in children is rapidly diminishing in favour of chemotherapy even when the tumour is very radiosensitive, e.g. in dysgerminoma. In intracranial MGCT, good results have been reported with the use of chemotherapy alone.[29]

Rhabdomyosarcoma

The prognosis of rhabdomyosarcoma (RMS) has improved considerably with multimodal therapy. The outcome is dependent on the site, the stage and the resectibility of the tumour as well as the histology. Results from successive Intergroup Rhabdomyosarcoma Studies (IRS) have confirmed the excellent 5-year survival rates, ranging from 93% (for localised, resected Clinical Group I disease) to 70% (for regional Group III tumour).[30,31] (Table 2) Refinement of treatment aimed at reducing toxicity but maintaining efficacy has been successful. The two-drug regimen (VA) using vincristine and actinomycin D (omitting cyclophosphamide) is adequate for Group I and II disease and radiotherapy can safely be omitted for Group I disease. Although VAC (VA and cyclophosphamide) is the tested combination for Groups III and IV as well as for RMS Groups I and II with the unfavourable alveolar histology, other effective drugs like VP-16, ifosphamide, adriamycin and cisplatinum are being tested. The prognosis of metastatic RMS remains relatively poor with a 5-year survival rate of only 27%.[31] The site of tumour is an important prognosis variable. Favourable sites include orbit, genitourinary tract except bladder and prostate (e.g. vulva, vagina, paratesticular), head and neck other than parameningeal sites.[31]

Osteosarcoma

In osteosarcoma, the use of neoadjuvant chemotherapy has not only increased the five-year relapse-free survival rates to 65-80% but has also permitted limb-salvage in as many as 80% of cases.[32,33] Indicators of poor prognosis

Table 2 IRS-III Findings

Clinical Group		Treatment	5y surv	Comment
I*	(localized, resected)	V, Act, 1y	93%	No CYC, RT; treatment maybe shorter
II*	(microscopic residual)	V, Act, 1y +RT (41 Gy)	73-89%	No ADR
III*	(gross residual ± N+)	VAC, 2y +RT	70%	Vastly improved from IRS-II
IV	(metastatic)	VAC, 2y +RT	27%	No change; ? ABMT needed

* FH, FS only; Bladder/prostate: VAC+ADR+CDDP+RT-WK6
(5-yr survival: 83%, from 72%; bladder salvage 60%, from 25%)
ALVEOLAR tumours, clinical Grp I, II: VAC+ADR+CDDP: 5-yr survival 80%, from 71%
FS: favourable site; ABMT: antigen BMT; ADR: adriamycin

include axial skeleton primaries, presence of pulmonary metastases at diagnosis and poor histologic response during induction therapy.

Ewing's Family of Tumours

The Ewing's family of tumours is a group of tumours derived from the primitive neuroectodermal cell with variable differentiation. Classical Ewing's sarcoma represents the poorly differentiated end of the spectrum presenting primarily as a bony tumour whereas peripheral primitive neuroectodermal tumour (pPNET) represents the other well differentiated end presenting primarily as a soft tissue tumour. However, they all share the same immunohistochemical staining profile and tumours all contain the unique chromosomal marker t(11;22).[34] The prognosis of Ewing's family of tumours also has improved greatly with multimodal therapy. Local control with either surgery or radiation is crucial to cure. Adjunctive chemotherapy is also very important and recent innovations in the use of drugs involving vincristine, actinomycin, high-dose cyclophosphamide, adriamycin, ifosphamide and VP-16 have resulted in long term EFS rates to increase to about 70-75%.[35]

Hepatoblastoma

Hepatoblastoma is a rare embryonal tumour occurring in the first 5 years of life, accounting for 1-2% of all childhood cancers. Surgical resectibility is the single most important prognosis factor. At diagnosis, about 50% are grossly resectable, 40% are localised but unresectable and 10% have metastases. It is chemosensitive and pre-operative adjuctive chemotherapy with cisplatinum and adriamycin renders the unresectable resectable. Cure rates with surgery and pre- and post-operative chemotherapy are in the region of 65-75%.[36,37]

Long Term Effects of Treatment

While the majority of children with cancer have achieved a biological cure and have their disease eliminated, many do not return to normal health due to the long-term effects of their disease or its treatment, broadly classified as medical and psychological. In addition, they encounter difficulties with education, employment or insurance. The medical consequences of their disease/treatment are found in many organ systems. Endocrine effects include growth failure from growth hormone deficiency caused by cranial irradiation given in the treatment of brain tumours or ALL. Other endocrine disturbances are pubertal disturbances, infertility or even early menopause caused by chemoradiotherapy. Examples of other long term sequelae are: cardiomyopathy due to anthracyclines; renal failure and tubular dysfunction caused by the use of cisplatinum and ifosphamide; significant long-term neuropsychological effects of cranial irradiation and growth retardation of bones and soft tissues in previously irradiated fields.[38] Survivors of childhood cancer also have to live with the fear of developing second cancers, either leukaemia (mainly AML) or solid tumours. The incidence of second malignant neoplasms (SMNs) either leukaemias or solid tumours, averages about 3% at 15 years from diagnosis, estimated to be 10-15 times greater compared to age-matched controls.[38-40] In one study, survivors of Hodgkin's disease were reported to have an 8% risk at 15 years of developing leukaemia and solid tumours in previously irradiated areas, this chance increasing to 18% at 20 years.[40] Children treated for ALL with epipodophyllotoxins have a cumulated 5-12% risk at 2-6 years of developing AML which is usually therapy-resistant.[41,42] Secondary solid tumours usually develop at sites of previous radiation e.g. in survivors of Ewing's sarcoma there is a 9% risk at 20 years of developing osteosarcoma in irradiated fields.[40] In addition, genetic factors are also important as can be seen in survivors of bilateral retinoblastoma who have a 38% chance at 30 years of developing osteosarcoma or soft tissue sarcoma, a risk which is greater than what is expected on the basis of previous irradiation.

The psychological cost of cure can also be far reaching. Children with cancer are often socially isolated by their peers, partly because of their personality change related to their illness. Many become more passive, depressed and introverted with loss of self-confidence. This problem is often compounded by stressed family relationships, e.g. sibling rivalry, parental marital discord and divorce. Their educational development is often impaired, due not only to direct intellectual impairment caused by their disease or its treatment, but also to frequent school absenteeism, truancy leading to their drop-out.

Future Challenges

Much remains to be done. Although 80% of children with cancer can be cured, a significant 20% still die of their disease. There is a small group of childhood cancers which are regarded as relatively resistant to treatment which should pose a real challenge in the new millennium. These include: 1. stage 4 neuroblastoma; 2. juvenile chronic myeloid leukaemia; 3. non-rhabdomyosarcoma soft tissue sarcomas; 4. metastatic disease at diagnosis; 5.

cancer subsets with bad prognostic features and 6. relapse of cancer, particularly during treatment. Many of the latter have developed drug resistance which even bone marrow transplantation often cannot correct. In treating cancers, it is important to observe the principle that 'the first chance is the best chance' for cure and not allow a relapse to occur. New ways must be found to cure them--- better drugs which are more efficacious but less toxic; more refined radiotherapy and surgical techniques and novel treatment strategies based on immunomolecular methods. Molecular techniques need to be developed for earlier and more precise diagnosis and classification of tumours as well as early detection of minimal residual disease and relapse. More accurate methods need to be devised to better identify prospectively within each cancer type subsets of tumour of varying risks so that treatment could be stratified to restrict the more intensive or toxic treatment to only the high-risk cases. Infection-associated deaths, still a major cause of mortality, can be further minimised if infections could be diagnosed earlier and more effectively treated by better antimicrobials. At present progress in the prevention of childhood cancer is virtually nil despite the wealth of new knowledge about molecular and cellular events leading to cancers. New research findings about cancer aetiology need to be translated to better methods of diagnosis and treatment and to help prevent childhood cancer. Finally, one may ask the question: if childhood cancer is curable, why are so many still not cured? This applies especially to those in less developed countries where the vast majority of the world's childhood cancer burden lies. For them, there are still many obstacles to cure and it would be a great challenge to the world in the new millennium to ensure that the best that is available in the treatment of cancer in children is applied to all.

Conclusion

The truly remarkable successes in paediatric oncology were achieved in the last 50 years of this millennium. In the new millennium the prospects for the child with cancer are bright indeed. New knowledge about the molecular basis of childhood cancer and an understanding of cancer aetiology offer the hope of a lasting cure for the disease --- a full restoration of normal health, not merely the elimination of cancer.

Acknowledgement

I wish to thank the Hong Kong Paediatric Society for giving me this great honour of delivering the C Elaine Field Lecture.

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