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Factors in Improved Survival from Paediatric Cancer

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Abstract

In 1998, over two-thirds of children diagnosed with cancer will be cured of their disease. This has been accomplished by improvements in understanding the biology of the various forms of cancer and stratifying protocol-based therapies (surgery, radiotherapy and chemotherapy) based on predicted treatment outcome and risk of treatment failure. The excellent prognosis of subgroups of malignancies, including acute lymphoblastic leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma and Wilms' tumour, has led to the modification of therapies to decrease or minimise long term adverse effects which may have a significant impact on the quality of life of survivors. The lessons learned from the treatment of paediatric cancer may lead to improvements in the treatment of adult cancers.

Significant progress has been made in the treatment of childhood cancer, with over two-thirds of newly diagnosed patients being cured of their disease; this is in contrast to 35 years ago, when only 28% of children became long term survivors.[1] This remarkable accomplishment has been achieved by a better understanding of the biology of the various forms of paediatric cancer and improvements in treatment, utilising surgery, radiotherapy and chemotherapy. The lessons that have been learned from the treatment of childhood cancer may provide insights into improving the treatment of adult cancers, which only recently have shown an overall improvement in survival rates.[2]

Paediatric cancers represent approximately 1% of total cancer cases in the United States, yet approximately 95% of children with cancer are registered, and 70% are treated, in multicentre clinical trials conducted by either the Pediatric Oncology Group (POG) or Children's Cancer Group (CCG) which are overseen by the National Cancer Institute, compared with only 2% of adult patients treated in clinical trials.[3]

The use of protocol-based therapy appears to have made a significant impact on cure rates by identifying the most appropriate treatments for a particular cancer,[4,5] along with monitoring for late effects of therapy in survivors. Multi-agent chemotherapy appears to be responsible for a significant proportion of the improvements in survival, as highlighted by progress in the treatment of acute lymphoblastic leukaemia (ALL),[1] the most common form of paediatric cancer.

This review highlights the current treatment of the major forms of childhood cancer and discusses factors responsible for improvements in survival. The current survival rates for paediatric cancers are shown in figure 1 and chemotherapy agents commonly used to treat them are listed in table I.

1. Treatment and Prognosis of Childhood Cancers

1.1 Acute Lymphoblastic Leukaemia

In 1948 Farber reported that the antifolate agent aminopterin produced temporary remissions in childhood ALL, providing initial evidence that a previously fatal disease was responsive to drug ther-

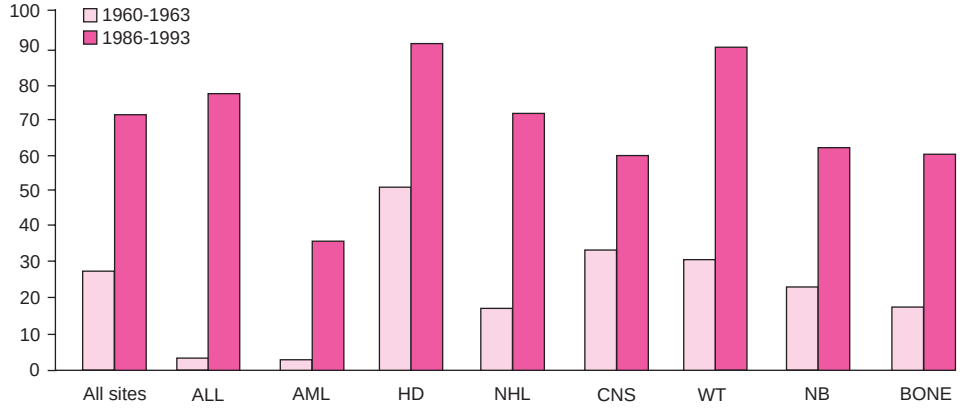

Fig. 1. Overall survival rates of childhood cancer for the time periods 1960-1963 and 1986-1993. **ALL** = acute lymphoblastic leukaemia; **AML** = acute myeloid leukaemia; **BONE** = bone tumours including osteosarcoma and Ewing's sarcoma; **CNS** = central nervous system tumours; **HD** = Hodgkin's disease; **NB** = neuroblastoma; **NHL** = non-Hodgkin's lymphoma; **WT** = Wilms' tumour.

apy.[6] The introduction of methotrexate, an antifolate less toxic than aminopterin, mercaptopurine and corticosteroids in the early 1950s, led to the first group of long term paediatric survivors of ALL.[7-9] The cental nervous system (CNS) became a common site of relapse in patients who remained in bone marrow remission; this led to the use of prophylactic therapy to prevent the development of CNS leukaemia, utilising either radiotherapy and/or intrathecal chemotherapy. Intrathecal chemotherapy is associated with fewer long term adverse effects compared with radiotherapy.[10]

Immunophenotyping of ALL blast cells with monoclonal antibodies is used to classify ALL into subtypes of either B lineage (85%; comprised almost entirely of B-precursor ALL) or T lineage (15%). Current treatments are based on leukaemia lineage, patient characteristics and biological features of the blast cells. B-precursor ALL can be stratified as either standard or high risk based on the probability of relapse and the risk rating is used as a determinant of treatment intensity required. Standard risk ALL includes patients between the ages of 1 to 9 years with a white blood cell count at diagnosis of <50 000/μl. This group is considered responsive to antimetabolite-based therapy.[11] T cell ALL is categorised as high risk and requires intensive therapy, including alkylating agents and anthracyclines.[12]

Acquired quantitative and qualitative chromosomal abnormalities in leukaemia cells are linked to leukaemogenesis and are of prognostic value. B-precursor ALL with hyperdiploid chromosomes (>50 chromosomes, DNA index >1.16) is a very favourable prognostic group and is very sensitive to antimetabolite-based therapy including methotrexate.[13,14] Intracellular accumulation of methotrexate polyglutamates (methotrexate-polyglutamates) *ex vivo* is a major determinant of methotrexate antileukaemic activity[15] and hyperdiploid ALL blast cells accumulate higher levels of methotrexate-polyglutamates compared with blast cells from patients with other aneuploid or diploid chromosomes.[13,15,16] Extra copies of chromosome 21 are present in up to 97% of cases of hyperdiploid ALL,[17] and the localisation of the reduced folate carrier gene (membrane protein for intracellular transport of methotrexate) to chromosome 21q22.3,[18] suggests that increased expression of the methotrexate transport gene in hyperdiploid ALL with acquired extra copies of chromosome 21,[19] may be responsible for the greater generation of methotrexate-polyglutamates.[20]

The recently identified translocation t(12;21), is the most frequent cytogenetic abnormality in childhood B-precursor ALL, being detected in over 20% of cases. ALL with t(12;21) has an excellent prognosis with antimetabolite-based therapy as for the

TABLE 1 TO GO HERE

LANDSCAPE

hyperdiploid ALL group, though the mechanisms of chemotherapy sensitivity have not been identified yet.[21,22]

Adverse cytogenetic abnormalities in B-precursor ALL include the t(9;22) and t(4;11) translocations,[23] while the prognosis for ALL with the t(1;19) translocation has improved with intensive therapy.[24] The breakpoint in t(4;11) occurs at 11q23, the site of the mixed lineage leukaemia (MLL) gene which is present in a high proportion of infant ALL cases and secondary leukaemias following epipodophyllotoxin therapy.[25]

Strategies currently being used to improve the treatment of T cell ALL include high-dose methotrexate (5 g/m^2 compared with 1 g/m^2 commonly used for B-precursor ALL),[26] consistent with the observations that T cell ALL blasts accumulate lower levels of methotrexate-polyglutamates compared with B-precursor blasts with the equivalent dose of methotrexate[16] and a high proportion of T-ALL blasts have elevated dihydrofolate reductase levels (target enzyme of methotrexate inhibition) at diagnosis.[27] Another treatment for T cell ALL is the investigational drug guanine arabinoside, a deoxyguanosine derivative which is selectively toxic to T-lymphoblasts.[28]

New approaches in the therapy of ALL include *in vitro* drug sensitivity testing utilising the MTT (3-[4,5-dimethyl-thiazol-2yl]-2,5-diphenyltetrazolium-bromide) assay to identify drug sensitivity or resistance at either diagnosis or relapse which can be used potentially to design patient-specific drug protocols.[29,30] The finding of residual leukaemia cells by polymerase chain reaction (PCR) techniques in bone marrow samples may be predictive of early bone marrow relapse several months before a clinical relapse is identified,[31,32] which may lead to the institution of alternative therapies at an earlier time-point.

1.2 Acute Myeloid Leukaemia (AML)

AML continues to have the worst prognosis of all major childhood cancers despite the use of intensive chemotherapy.[1,33] Matched related allogeneic bone marrow transplants for AML in first

Table I. Chemotherapeutic agents currently in use for the treatment of childhood cancer[a]

Type of cancer	Pred	VCR	L-ASP	6-MP	MTX	ARA-C	CPM	IFOS	CPPD	CBDCA	ACD	VP-16	DOX	DNR	BCNU
Acute lymphoblastic leukaemia	+	+	+	+	+	+	+					+	+		
Acute myeloid leukemia						+						+		+	
Hodgkin's disease[a]	+	+					+					+	+		
Non-Hodgkin's lymphoma	+	+	+	+	+	+	+					+	+		
CNS cancers		+					+	+	+	+		+			+
Wilm's tumour		+					+				+		+		
Neuroblastoma		+					+	+	+	+		+	+		
Retinoblastoma		+								+		+			
Rhabdomyosarcoma		+					+	+	+		+	+	+		
Osteosarcoma					+		+		+				+		
Ewing's sarcoma		+					+	+			+	+	+		

a Hodgkin's disease treatment also includes chlormethine (nitrogen mustard), vinblastine, procarbazine, bleomycin and dacarbazine. Radiotherapy is also utilised in the treatment of acute lymphoblastic leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, brain tumors, Wilm's tumour, retinoblastoma, rhabdomyosarcoma and Ewing's sarcoma.

6-MP = 6-mercaptopurine; **ACD** = actinomycin; **ARA-C** = cytarabine; **BCNU** = carmustine; **CBDCA** = carboplatin; **CPM** = cyclophosphamide; **CPPD** = cisplatin; **DNR** = daunorubicin; **DOX** = doxorubicin; **IFOS** = ifosfamide; **L-ASP** = l-asparaginase; **MTX** = methotrexate; **Pred** = prednisone; **VCR** = vincristine; **VP16** = etoposide.

remission are considered superior to chemotherapy, although this approach is limited by the lack of suitable transplant donors for many patients.[30]

As in ALL, certain cytogenetic abnormalities in AML have a favourable prognosis including: (i) acute myeloblastic leukaemia (M2) with t(8;21), which is responsive to high dose cytarabine therapy;[34] (ii) acute promyelocytic leukaemia (M3) with t(15;17) in which there is fusion of the promyelocytic gene with the retinoic acid receptor alpha gene;[35] the resulting fusion protein allows for the differentiation of leukaemic promyelocytes into mature cells by tretinoin; and (iii) acute myelomonocytic leukaemia (M4) with inv(16) resulting in deletion of the multi-drug resistance associated protein (MRP) gene (localised to chromosome 16 p13.1) which is associated with longer remission durations than cases of inv 16 without deletion of the MRP gene.[36] AML with inv(16) is also responsive to cytarabine therapy.[34]

Down's syndrome (trisomy 21) children with AML have the highest cure rates of any subgroup of patients with AML, with event-free survival rates of 68 to 100% using treatments which include daunorubicin and high-dose cytarabine.[33,37] Down's syndrome myeloblasts are significantly more sensitive *in vitro* to both cytarabine and daunorubicin compared to non-Down's syndrome myeloblasts and generate significantly higher levels of the active intracellular cytarabine metabolite ara-CTP.[37,38] The biological basis for these findings include the increased expression of the chromosome 21-localised genes cystathionine-β-synthase and superoxide dismutase in Down's syndrome myeloblasts which correlates with *in vitro* sensitivity to cytarabine.[39] Additional analysis of the mechanisms of chemotherapy sensitivity of patients with Down's syndrome with AML may provide insights into improving AML therapy for all patients.

1.3 Hodgkin's Disease (HD)

The introduction of the MOPP [chlormethine (nitrogen mustard), vincristine, prednisone, procarbazine][40] and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimens and hybrid regimens using both protocols with or without radiotherapy have resulted in HD being one of the most curable cancers in children.[1,41] Patients who fail initial treatment with radiotherapy alone can often be salvaged with chemotherapy, whereas patients who fail conventional chemotherapy with or without radiotherapy may respond to high dose therapy with autologous bone marrow/peripheral stem cell support.

In view of the very high cure rates achieved in children with HD, attention has now turned to minimising long term effects of therapy associated with the use of alkylating agents (secondary malignancies and infertility) and radiotherapy (solid tumours including an increased risk of breast cancer in female survivors).[42-46] Dexrazoxane, an agent which chelates intracellular iron and protects against anthracycline-induced cardiotoxicity,[47] is being utilised by the POG to minimise the cardiotoxicity of doxorubicin[48] and pulmonary toxicity of bleomycin. The use of staging laparotomy with splenectomy (associated with an increased risk of overwhelming sepsis with encapsulated bacteria) is being utilised less often,[41] as the documentation of microscopic abdominal disease is less critical with chemotherapy-based treatments.

1.4 Non-Hodgkin's Lymphoma

Paediatric non-Hodgkin's lymphomas are generally diffuse aggressive lymphomas compared with the low grade indolent lymphomas commonly observed in adults and are more responsive to intensive therapy. Therapies are based on disease stage, histology of the tumours and whether they are of B cell or T cell origin.[49,50] The prognoses for Burkitt's lymphoma and mature B cell ALL have improved significantly with the use of intensive short courses of therapy using alkylating agents and antimetabolites and aggressive supportive care to manage tumour lysis syndrome.[51,52] Localised small cell lymphomas can be successfully treated with short courses of therapy of as little as 9 weeks' duration,[53] while lymphoblastic

lymphomas of T cell origin are treated in a similar fashion to T cell ALL.[50]

1.5 Brain Tumours

The primary treatment of brain tumours usually involves surgical resection (depending on the size and location of the tumour) and radiotherapy.[54] Radiotherapy may be curative, but it is associated with significant long term neuropsychological and endocrine abnormalities, particularly in young children. Multi-agent chemotherapy is gaining wider use as an additional treatment modality, particularly in young children (aged <3 years) to delay the use of radiotherapy and potentially minimise late neuropsychological effects.[55] Several types of tumours known to be sensitive to chemotherapy include medulloblastomas, ependymomas and CNS germ cell tumours.[54] Recurrent brain tumours have been successfully treated with high dose therapy with autologous bone marrow support.[56] Gene therapy is a promising future option in this setting.[57]

1.6 Wilms' tumour

Since the initiation of the first National Wilms' Tumour Study in 1969, significant advances in the staging, surgical resection and pathological grading of tumours (favourable or unfavourable) have resulted in Wilms' tumour being one of the most curable paediatric tumours, even in patients with metastatic disease.[1,58] These studies have identified that patients with low stage disease can be treated successfully with postoperative chemotherapy alone, whereas patients with more advanced disease are responsive to combined chemotherapy and radiotherapy.

1.7 Neuroblastoma

Prognostic stratification of neuroblastoma predictive of treatment response includes patient age, tumour ploidy and copy number of the n-myc oncogene (normal or amplified).[59] Low risk patients (age <1 year, hyperdiploid karyotype, normal n-myc copy number) may require surgery alone while high risk patients (age >1 year and n-myc amplification) require intensive therapy.[59] The majority of patients diagnosed after the age of 1 year have stage III/IV disease in which survival appears superior with high dose therapy with stem cell support compared with standard dose chemotherapy alone. Isotretinoin (13-cis-retinoic acid) therapy has been shown to reduce the risk of recurrence in high risk patients treated with intensive chemotherapy and/or autologous bone marrow transplantation.[60] New therapies to salvage patients with recurrent disease include the monoclonal antibody anti-GD2[61,62] and radioactive metaiodobenzylguanidine (MIBG).[63]

1.8 Retinoblastoma

Although not well defined until recently,[64] multi-agent chemotherapy, including carboplatin, used in conjunction with local therapy (cryotherapy, laser therapy and brachytherapy) is being used to treat bilateral retinoblastoma and selected cases with unilateral disease, resulting in preserved vision.[65-68] This new approach is replacing previously used curative approaches which had significant late effects associated with eye enucleation and/or use of external beam irradiation which increases the risk of secondary malignancies (osteosarcoma and soft tissue sarcomas) in patients with germline mutations of the retinoblastoma gene (present in every case of bilateral disease).[69,70]

1.9 Rhabdomyosarcoma

The Intergroup Rhabdomyosarcoma Study group has identified that the site, stage and histologic grade of the tumour has a major bearing on outcome and response to combined therapy with surgery, chemotherapy and radiotherapy.[71] Favourable tumour sites include the orbit, head and neck (excluding parameningeal region) and paratesticular regions. The prognosis for tumours with alveolar histology and tumours arising from the extremities has improved with intensified therapy.[71]

1.10 Osteosarcoma/Ewing's Sarcoma

The presence of micrometastatic disease at presentation of both osteosarcoma and Ewing's sarcoma indicate that surgical resection alone is insufficient for tumour control, necessitating the use of systemic therapy.[72,73] Both of these tumours are sensitive to chemotherapy (Ewing's sarcoma is also sensitive to radiotherapy) and initial chemotherapy is commonly used to shrink the tumours, followed by tumour resection. This technique may allow the limb to be salvaged without amputation.[74,75] New imaging modalities including positron emission tomography (PET) technology have been able to identify tumour viability following chemotherapy and prior to surgical resection.[76] Higher disease-free survival rates have been found to correlate with greater degrees of tumour necrosis.[77]

2. New Agents and Supportive Therapies

Promising new agents are continually being tested in phase I trials of paediatric cancers.[78] Agents which appear promising at present include topotecan and paclitaxel.[79,80]

Haematopoietic growth factors including granulocyte colony-stimulating factor (G-CSF) have been utilised to shorten the duration of neutropenia following myelosuppressive chemotherapy, potentially decreasing the risk of infection and allowing for the intensification of therapy.[81] New growth factors in development include megakaryocyte growth and development factor (MDGF) and interleukin-11, which stimulate platelet production and reduce the need for platelet transfusions.[82,83]

Future protocols may include the use of amifostine (WR-2721), developed initially as a radiation protector, which scavenges free radicals and preferentially protects normal cells from chemotherapy-related toxicities including myelosuppression, neurotoxicity, nephrotoxicity and ototoxicity without compromising the antitumour effect of chemotherapy drugs.[84,85]

3. Long Term Effects of Therapy

The success in the treatment of childhood cancer has to be tempered with the realisation that significant long term effects of therapy (chemotherapy, radiotherapy or a combination of both) may have an impact on the quality of life of survivors[86] (table II). The concern that the offspring of childhood cancer survivors may have an increased risk of cancer or birth defects has not been substantiated in several large cohort studies of childhood cancer survivors.[87-89]

4. Conclusions

The significant progress made in the treatment and cure of childhood cancer is nothing short of impressive and reflects the concentrated effort of both basic researchers and clinicians to better understand the biology of the various forms of cancer and to coordinate multicentre clinical trials, in order to identify the most appropriate forms of therapy. The identification of late effects of therapy may allow for the modification of treatments to minimise these effects so that patients can lead healthy productive lives as adults. Continued improvements in understanding the biological basis of cancer will lead to an increased number of survivors and can possibly result in strategies to prevent cancer from developing in children.

Table II. Late effects of cancer therapy

Cardiac toxicity (doxorubicin, daunorubicin, radiation)
Pulmonary toxicity (bleomycin, carmustine, methotrexate, radiation)
Renal/bladder toxicity (cisplatin, ifosfamide, cyclophosphamide, carboplatin)
Ototoxicity (cisplatin)
Infertility (alkylating agents, radiation)
Neuroendocrine toxicity (radiation)
Cognitive function impairment (radiation, methotrexate)
Growth retardation (radiation)
Thyroid toxicity (radiation)
Visual toxicity (radiation)
Secondary malignancies (alkylating agents, epipodophyllotoxins, radiation)
Discrimination in obtaining employment, health and life insurance

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