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Treatment of Paediatric Cancers in Hong Kong: An Interim Report

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Abstract The Hong Kong Paediatric Haematology and Oncology Study Group conducted clinical studies on treatment of various paediatric cancers in Hong Kong. This article reported the treatment result of the various cancers presented in the annual workshop in February 2000. The five-year overall survival and event free survival were 80.2% and 62% for Acute Lymphoblastic Leukaemia, and were 60% and 53% for Acute Myeloid Leukaemia respectively. The other cancers with shorter follow up had three years overall and event free survival as follow: 75% and 62% for Medulloblastoma, 74% and 67% for Non-Hodgkin Lymphoma, 100% and 91% for extracranial Germ Cell Tumour, 30% and 20% for advanced neuroblastoma, 68% and 52% for Ewing's Sarcoma, 87% and 79% for Wilms' Tumour, 82% and 80% for Osteosarcoma, 56% and 45% for Rhabdomyosarcoma, and 60% and 50% for Hepatoblastoma respectively. The protocols had a high rate of adoption by the various hospitals, over 95% eligible patients were treated according to protocols. The toxicity of these protocols was acceptable with treatment related mortality less than 5% in most protocols.

Key words Overall and event free survival

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Introduction

The Hong Kong Paediatric Haematology and Oncology Study Group (HKPHOSG) was formed in 1993. The members are doctors working in public hospitals of Hospital Authority (HA) with experience in management of paediatric haematology and oncology patients. Since formation of the Study Group, treatment protocols have been set up for various childhood cancers and are adopted by the members. These protocols are adopted from large clinical trials of European and North American studies. Since the number of patients of various childhood cancers is usually small, it is not possible to run our own randomised clinical trials. Using uniform treatment protocols in all public hospitals has the advantage of more efficiently gaining experience among the local paediatric oncologists. Regular monthly meetings are held to share experience among the members. An annual workshop aims at reviewing the progress and evaluating the treatment outcome. This article highlights the progress report of the annual workshop held in February 2000. The hospitals participated in the studies include Caritas Medical Centre, Prince of Wales Hospital, Princess Margaret Hospital, Queen Elizabeth Hospital, Queen Mary Hospital and Tuen Mun Hospital.

Method and Result

The studies with greater number of patients recruited or with longer follow up were presented in greater details. The other studies would be presented in brief and the results were shown in the Table 1. The study protocols had a high rate of adoption by the participating hospitals with most studies approaching 100%. Osteosarcoma protocol had the lowest adoption rate with only 83% eligible patients treated according to study protocol. The modification of the current protocols from the original studies was presented in Table 2. The types of cancers collected by the HKPHOSG from 1993 to 1999 were shown in Table 3. The Hong Kong Cancer Registry has

Table 1 Treatment result of HKPHOSG studies and comparison with other studies[14-16,18]

	Number of patients	HKPHOSG			Other studies			
		OS	EFS	Treatment mortality	Original studies	OS	EFS	Ref.
ALL 93*	152	80.2%	62%	3.3%	MRC ALL XI	85%	60%	2
AML*	49	60%	53%	6.1%	MRC AML 10	56%	48%	7
Medulloblastoma	27	75%	62%	0	CCG °	55%	54%	14
Non-Hodgkin's Lymphoma	43	74%	67%	6.9%	LMB 84	79%	78%	8
Germ Cell Tumour	39	100%	91%	0	UKCCSG	96%	98%	11
Stage 3/4 Neuroblastoma	15	30%	20%	7%	CCG °	45%	30%	15
Ewing's Sarcoma/PNET	24	68%	52%	0	UKCCSG °	62%	56%	16
Wilms' Tumour*	46	87%	79%	4.3%	NWTS 4	95%	87%	17
Osteosarcoma	24	83%	80%	0	MSKCC T12 °	-	73%	18
Rhabdomyosarcoma	30	56%	45%	3%	IRS III	71%	65%	12
Hepatoblastoma	16	60%	50%	0	POG	-	67-91%	13

* Five-year survival of the local studies. The other local studies were reported as three-year survival.

° Not the original studies, but these are studies with most similar approach shown.

OS=overall survival, EFS=event free survival, ALL=acute lymphoblastic leukaemia, AML=acute myeloid leukaemia.

Table 2 Modification from original studies

HKPHOSG	Original studies	Major modification
ALL	MRC ALL XI	• Not randomizing patients for 3rd intensification, • 3rd intensification was only given to high risk patients.
AML	MRC AML X	• Not randomizing patients to thioguanine vs etoposide. • All patients received etoposide.
Wilms' Tumour	NWTS	• Not randomizing patients to long treatment vs short treatment courses. • All patients treated with long treatment.
Rhabdomyosarcoma	IRS IV	• Not randomizing patients to Ifosfamide vs Cyclophosphamide. • All patients received Ifosfamide.

Table 3 Types of childhood cancers treated by HKPHOSG (1993 to 1999)

	Number	% of whole group
Acute Lymphoblastic Leukaemia	214	24.3%
Acute Myeloid Leukaemia	64	7.3%
Chronic Leukaemia / MDS	39	4.4%
Brain Tumour	130	14.8%
Non-Hodgkin's Lymphoma	53	6.0%
Neuroblastoma	54	6.1%
Osteosarcoma	31	3.5%
Wilms' Tumour	27	3.1%
Rhabdomyosarcoma	50	5.7%
Ewing's Sarcoma	10	1.1%
Liver Tumour	41	4.7%
Germ Cell Tumour	45	5.1%
Others	122	13.9%
	880	100%

more complete data on cancer patients diagnosed in the HKSAR, the incidence of childhood cancers should be referred to the Annual Reports from Hong Kong Cancer Registry.[1] The cancer incidence in years 1993 to 1996 is 129 per million population below age of 15 years.

Acute Lymphoblastic Leukaemia (ALL)

Two studies have been conducted on ALL since 1993. The first study started in 1993 and ended in October 1997 (HKALL 93). The second study started from November 1997 and is still opened for recruitment (HKALL 97).

HKALL 93: This protocol was modified from the United Kingdom Medical Research Council (UK MRC) ALL XI Study.[2] The objective was to study outcome of non-high risk patients treated without prophylactic cranial irradiation. A total of 152 patients were entered into this study. Patients were stratified according to age, initial white cell counts, immunophenotyping and cytogenetics of leukaemia cells. The patients were classified into standard risk (39%), intermediate risk (32%) and high risk (29%). Only high risk patients with WBC >50 x 10^9/L or T-cell ALL or Philadelphia chromosome received prophylactic 18 Gy cranial irradiation. The induction remission rate was 96.7% and the induction death rate was 2%. Two patients (1.3%) died from treatment complication while in first complete remission. Relapses had occurred in 31.5% of patients, and bone marrow was the most common site of relapse (21.7%). Isolated central nervous system (CNS) relapse occurred in 5.2% of the whole group, but in 10% of intermediate risk patients. Up to February 2000, 122 patients (80%) were still alive and 94 (62%) were in first complete remission. With a median follow up of 47 months (range 24 to 85 months), the projected five-year overall survival (OS) and event free survival (EFS) of the whole group was 80.2% and 62% respectively. The EFS for standard risk, intermediate risk and high risk was 77.7%, 53% and 51.4% respectively. In conclusion, the overall EFS was similar to the MRC study. The CNS relapse rate for the whole group was acceptable but appeared to be high in the intermediate risk group.

HKALL 97: This study was started from November 1997 and is still recruiting new patients. This is a study that changed the tradition of following UK ALL trials of the past two decades to a German approach. The interim analysis of the HKALL 93 study suggested that the overall result was inferior to other cooperative groups. Most groups now reported a five-year EFS of 70% to 80%.[3-5] The German group (BFM Study) has reported one of the best treatment results for childhood ALL with EFS of 78%.[5,6] The HKPHOSG decided to follow the German approach and designed the new HKALL 97 study. The objective was to improve the overall result of the ALL with more intensive treatment. This is a prospective study with ethical approval from HA and required written informed consent. Central review of the bone marrow and cytogenetic study was performed to ensure accuracy of the cases. Molecular analyses of all diagnostic specimens were also performed with the financial support from the Children's Cancer Foundation. National University Hospital of Singapore also joins in this multicentre study. Up to February 2000, 84 patients were recruited. The remission rate was 96.5% and one patient died during induction. So far two patients relapsed in the bone marrow. There were two treatment-related deaths during the first complete remission. The patients' characteristics of this study were comparable with that of HKALL 93.

Acute Myeloid Leukaemia (AML)

The Study Group started a common treatment protocol for AML from 1994. The protocol was modified from the UK MRC AML 10 trial,[7] and later was further modified following the MRC AML 12 trial. The protocol consisted of four to five courses of very intensive induction and consolidation treatment over four to six months. Maintenance chemotherapy was not required. Allogeneic BMT would be performed in non-good-risk patients during first complete remission if compatible family donor was available. Up to December 1998, 49 patients were recruited in this protocol, and seven of them had Downs Syndrome. Four patients (8.1%) however died of intracranial haemorrhage before initiation of chemotherapy. Remission was achieved in 44 patients, 89.7% for all recruited patients or 98% for those who received induction chemotherapy. One patient died of refractory leukaemia and three (6.1%) died of complications after achieved remission. There were 12 bone marrow relapses (24.5%). CNS relapse was not observed. Up to February 2000, 26 patients (53%) survived in first continuous complete remission at median follow up of 32 months (range 13 to 67 months). Twenty-three patients received BMT, three were autologous BMT while the others received family donor or unrelated donor transplant. Ten of the 13 patients transplanted in the first complete remission remained in remission and four of the eight patients transplanted in second remission survived in remission. The five-year OS and EFS for the whole group were 60% and 53% respectively. In conclusion, the early result of intensive chemotherapy with or without transplant was encouraging and about half of the patients could be cured.

Non-Hodgkin Lymphoma (NHL)

NHL is the third commonest childhood malignancy. A common treatment protocol was started from January 1995 and 43 patients were recruited up to February 2000. T cell NHL was treated according to the ALL protocol of the same period. The B cell NHL was treated using a protocol modified from the UKCCSG which was based on a French study.[8] Forty-three patients were diagnosed with male predominance (72%). The mean age at diagnosis was eight years. Four patients had underlying immunodeficiency syndrome. According to histology, 32.6% were lymphoblastic, 20.9% Burkitt's and 32% of Large Cell. The staging of NHL was 7% Group A, 48.8% Group B, 9.3% Group C and 34.9% Group D. Complete remission was achieved in 83.7%, and there were three treatment related deaths. Relapses occurred in five patients (11%) and 30 patients were surviving in remission. There were three patients lost to follow up. The three-year OS and EFS were 74% and 67% respectively. After excluding patients with underlying immunodeficiency, the EFS was 75%. Lymphoblastic and Burkitt's NHL have better event free survival than Large cell NHL (100% and 80% vs 55%). In conclusion, the current protocols were effective for lymphoblastic and Burkitt's NHL. A more effective protocol for Large cell NHL would be required.

Neuroblastoma

From 1990 to February 2000, 61 patients were diagnosed as neuroblastoma. The annual incidence of neuroblastoma was thus 5.2 per million children below 15 years. Majority of the cases were diagnosed below age of five years (82%), and 30% were below one year. The commonest site of tumour was intra-abdominal, either adrenal or retroperitoneal. Most of the patients were diagnosed at advanced stages: 8.2% stage 1, 8.2% stage 2, 13.1% stage 3, 65.6% stage 4 and 4.9% stage 4S. The Study Group started a common treatment protocol (NB-95) for stage 3 and 4 neuroblastoma from January 1995 and closed in December 1998. This protocol was modified from the N6 protocol of the Memorial Sloan Kettering Cancer Center (MSKCC)[9] and aimed at improving the outcome of advanced neuroblastoma by intensive chemotherapy and autologous stem cell transplant. Fifteen patients were recruited into this protocol. Complete remission and good partial response could be achieved in all patients. Two patients died during treatment and one died of complication while in remission. With a median follow up of 30 months, five patients still survived but only three were in continuous remission. Despite a better survival at two years as compared to previous protocols (ie. OPEC), the projected three-year progression free survival remained poor at 20%. A new protocol was started from January 1999 that was modified from the N7 protocol of MSKCC. The objective of this protocol was to study the effectiveness of monoclonal antibody (3F8) in improving the outcome of patients with advanced stage neuro-blastoma. The rationale was to use immunotherapy to achieve better eradication of cancer cells for patients already treated with very intensive chemotherapy. This expensive monoclonal antibody was sponsored by generous donation through The Children's Cancer Foundation. Six patients were recruited into the study and the follow up was still short to make any conclusion. In conclusion, the very intensive chemotherapy including autologous stem cell transplant could prolong survival of the advanced stage patients but did not improve the final survival. The result of immunotherapy requires a longer follow up for evaluation.

Osteosarcoma

Osteosarcoma occurs more commonly at the adolescent age group. From November 1993, a common protocol was initiated in collaboration with adult oncologists. Twenty-nine children were diagnosed at the median age of 11.4 years. The commonest sites were around the knee, 16 over distal femur, seven at proximal tibia and one at proximal fibula. Six patients had pulmonary metastasis at time of diagnosis, and the others had localised disease. Twenty-four patients were treated according to the standard protocol and the outcome was analysed. The patients were treated with pre-operative chemotherapy followed by surgical resection and then post-operative chemotherapy. Limb salvage operation by bone allograft was attempted in 90% of patients. Only two patients were treated by amputation. There were five relapses, one at local tumour bed and three at lung and one with multiple relapses. With a median follow up of 36 months, the three-year OS and EFS were 82% and 80% respectively. In conclusion, the current chemotherapy protocol achieved adequate systemic and local control. Limb salvage operation was possible in majority of patients.

Other Solid Tumours

Brain tumour is the second commonest group of childhood tumour. A total of 116 patients were diagnosed between January 1995 to February 2000. Medulloblastoma (MB) was the commonest histology (20.7%) followed by germ cell tumour (15.5%) and brain stem glioma (14.8%). Twenty-seven medulloblastoma patients were treated

according to a common protocol.[10] The three-year overall survival and progression free survival were 75% and 62% respectively, at a median follow up of 22 months. **Extracranial Germ Cell Tumour** (GCT) is another common group of childhood cancer. Thirty-nine patients were diagnosed from January 1995 to February 2000. Gonads were the commonest sites (48.8%) followed by the sacrococcygeal region (20.5%). Teratoma and yolk sac tumours were the commonest histology. A common chemotherapy protocol was started from January 1995 modified from an UK protocol.[11] The survival was excellent for GCT with three-year OS and EFS of 100% and 91% respectively.

Ewing's Sarcoma (EWS) and peripheral Primitive Neuroectoderaml Tumour (pPNET) are now grouped under the umbrella of Ewing's Sarcoma Family of tumour because both ES and pPNET have the same cytogenetic abnormality. Eleven patients were histologically diagnosed as ES and 22 histologically diagnosed as pPNET. The primary sites were very heterogenous, from head and neck region to extremities or even various visceral organs. A significant proportion of patients had persistent disease or relapse after treatment and the three-year EFS was only 52%. **Wilms' tumour** is uncommon in children and only 46 patients were diagnosed in the past 10 years. Most of the patients were diagnosed at early stage and favourable histology was observed in 80%. Patients were treated with surgery and chemotherapy; and radiotherapy was included for advanced stage. The five-year OS and EFS were 87% and 79% respectively. **Rhabdomyosarcoma** has a wide diversity in the sites of occurrence, from head and neck region to extremities and intra-abdominal cavity. Thirty patients were diagnosed since August 1995 and were treated with a common protocol modified from the Intergroup Rhabdomyosacoma Study of North America.[12] Complete remission was only achieved in 67% after chemotherapy and surgical resection. The three-year OS and EFS were 56% and 45% respectively. For stage 4 patients, only 20% remained in remission.

From June 1996 to February 2000, 16 patients were diagnosed to have **hepatoblastoma** and treated according to a common protocol.[13] The median age of presentation was seven months (range three to 33 months) and mostly presented with abdominal distension. One patient had underlying Beckwith-Weideman syndrome. Five patients had primary resection of tumour at diagnosis and three had delayed resection after initial chemotherapy reduction. Six remained unresectable after initial chemotherapy. **Hepatocellular carcinoma** was diagnosed in 11 patients. The median age of presentation was 10.5 years (range five to 14). At diagnosis, seven patients were HBsAg positive and six of their mothers were known to be HBsAg positive. Only two patients survived in complete remission.

Conclusion

The protocols adopted by the Study Group have a high rate of adoption by the participating hospitals, over 95% in most protocols. The acute toxicity of these protocols was acceptable and treatment related mortality was low, less than 5% in most protocols. AML had a higher treatment related mortality of 6.1% due to more intensive treatment. However intensive treatment is required to achieve better event free survival, a significant improvement is demonstrated as compared to a previous local study, 53% versus 26%.[19]

ALL has the largest number of patients recruited. The HKALL 93 study showed that the result was quite comparable with the same treatment arms of original UK trial, EFS of 62% and 60%. The HKALL 93 does not show improvement in EFS as compared to a local study done in late 1980s based on an earlier version of MRC trial, 62% versus 67%.[20] However the HKALL 93 study can spare 70% of patients from cranial irradiation and thus reducing the late neurological complication. One of the main targets of cancer treatment is to improve the quality of life in long term survivors in addition to high cure rate. The UK ALL study had inferior EFS as compared to other European or American ALL studies.[3-5] The interim analysis showed unsatisfactory result of HKALL 93, the HKPHOSG thus decided for earlier switching to a German approach, HKALL 97 study, aiming at improving the outcome of our ALL children to the "world" standard. We still have to wait for few years to ascertain the outcome. The UK AML trial is one of the best among all childhood AML trials. The HK AML study also achieved similar result as the UK trial, and the same approach will be continued until new advances showing further improvement. The Germ cell tumour study achieved good results as compared to other studies because of chemo-responsiveness of the tumour. The result of osteosarcoma is encouraging and the EFS is comparable to study showing the best result.[17] Limb salvage operation can be achieved in a high proportion of patients. The other studies have relatively few patients and short follow up, and the staging and histology are also heterogeneous. Comparison with the original studies would be difficult.

The annual workshop serves the purpose of auditing the conduct of the protocols. Interim analysis of outcome of the various studies is important for monitoring toxicity and failure. Amendment or change of protocol will be made earlier if the preliminary result is unsatisfactory. Collaboration among the members is essential for the successful monitoring of these protocols. In the future, the Study Group will also participate in some international randomised studies, especially diseases with small number of patients locally.

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