Osteonecrosis in Adolescents and Young Adults with Acute Lymphoblastic Leukaemia on Hong Kong-Singapore Acute Lymphocytic Leukaemia 97 Protocol

Dear Editor,

Osteonecrosis (ON), a debilitating disease frequently involving multiple joints, has been recognised in recent years as a severe complication of acute lymphocytic leukaemia (ALL) therapy in adolescents and young adults. It hence presents a challenging obstacle in modern chemotherapy.[1]

There are several well-known risk factors for the development of ON, including the use of dexamethasone, age over 10 years and the female gender.[2,3] Another possible factor is the presence of certain genetic polymorphisms, such as in the *ACP1* gene (a regulator of lipid levels and osteoblast differentiation)[4] or *BMP7* gene (the BMP7 protein product is known to be toxic to bone vasculature).[5]

Other studies have also shown that high body mass index, low albumin levels and elevated cholesterol can be linked to ON.[4] The precise mechanism by which ON develops still remains unknown but administration of corticosteroids has been shown to cause ischaemia and induce excessive apoptosis of osteoblasts and osteocytes.[6]

In studies conducted in the United States and Europe, the overall incidence of ON in childhood ALL patients was highly variable, ranging from 1% to 9%.[1-3] A study conducted by the Japanese Childhood Cancer and Leukemia Study Group found an overall ON incidence of 1.5%,[7] comparable to previous studies. This study additionally found a significant correlation between age and ON incidence, with incidence rates of 0.42% for age less than 10 years versus 15.6% for age 10 years and above ($P < 0.0001$). This suggests that adolescents and young adults are at much greater risk of ON as compared to younger age groups.

One suggestion is that alternate-week steroid scheduling, instead of continuous, is a feasible way to prevent treatment-related ON.[8] However, empirical therapy for childhood ALL patients with ON is still lacking, due to a paucity of good quality studies. Greater understanding of individual risk factors and the underlying physiology in adolescents and young adults is still needed to improve prediction and management of ON in this population.

In this study, a retrospective analysis of adolescents and young adults aged 13 to 21 years with ALL, diagnosed and treated at a large tertiary hospital's haematology department, was conducted. These patients were treated with the Hong Kong-Singapore (HK-SG) 97 protocol, a Berlin-Frankfurt-Munster (BFM)-based, paediatric-inspired protocol. We aimed to evaluate the incidence and outcomes of ON within this population while outlining some recommendations to mitigate this problem.

Materials and Methods

From January 2009 to December 2014, all adolescents and young adults aged 13 to 21 years and newly diagnosed with ALL were treated with the HK-SG 97 regimen (Table 1). This diagnosis was made according to the World Health Organisation 2008 criteria, involving assessment of bone marrow morphology, karyotyping and molecular studies for *BCR/ABL* translocation. A retrospective review of the data was conducted from the Leukemia Registry and was approved by the institutional review board.

The HK-SG 97 protocol was previously used by the Hong Kong Paediatric Haematology and Oncology Study Group in a study of paediatric patients.[9] Patients are classified as high-risk if they have one of the following characteristics: 1) t(9;22) or *BCR-ABL* fusion; 2) t(4;11) or *MLL-AF4* fusion; 3) resistance to prednisolone, defined as absolute peripheral blast count >1 x 10^9/L on day 8 of pretreatment phase with prednisolone; and 4) ≥5% blasts in bone marrow on day 33 of induction phase 1A. All other patients are classified as intermediate risk.

Results

A total of 16 patients, 9 males (56%) and 7 females (44%), met the diagnostic criteria for ALL. Median age at diagnosis was 19 years. In our patient cohort, 62.5% of the patients were categorised as intermediate risk and the remaining 37.5% as high risk.

Of the 16 patients, 5 (31.3%) developed ON. Four were from the intermediate risk group. One of the 5 patients had ON diagnosed during salvage therapy and the other 4 were diagnosed during maintenance therapy. Of these 5 patients, 4 were male and 1 was female.

Bilateral ON of the hip, involving the femoral heads, was found in 4 patients, 3 of whom needed total hip replacement, while the other received no intervention as she succumbed

Table 1. Hong Kong-Singapore (HK-SG) 97 Protocol

Intermediate Risk	Day of Chemotherapy	High Risk	Day of Chemotherapy
Pretreatment		Pretreatment	
Prednisolone 20 mg/m^2 (PO)	1	Prednisolone 20 mg/m^2 (PO)	1
Prednisolone 40 mg/m^2 (PO)	2	Prednisolone 40 mg/m^2 (PO)	2
Prednisolone 60 mg/m^2 (PO)	3 – 7	Prednisolone 60 mg/m^2 (PO)	3 – 8
MTX 12 mg (IT)	Once	MTX 12 mg (IT)	Once
Induction 1A		Induction 1A	
Danorubicin 30 mg/m^2 (IV)	8, 15, 22, 29	Danorubicin 30 mg/m^2 (IV)	8, 15, 22, 29
Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29	Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29
Prednisolone 60 mg/m^2 (PO) then taper	8 – 28	Prednisolone 60 mg/m^2 (PO) then taper	8 – 28
L-asparaginase 5000 IU/m^2	12, 15, 18, 21, 24, 27, 30.33	L-asparaginase 5000 IU/m^2	12, 15, 18, 21, 24, 27, 30.33
MTX + Cytarabine + Hydrocort (IT)	15, 33	MTX + Cytarabine + Hydrocort (IT)	15, 33
MTX + Cytarabine + Hydrocort (IT)*	8, 22	MTX + Cytarabine + Hydrocort (IT)*	8, 22
Induction 1B		Induction 1B	
Cyclophosphamide 1000 mg/m^2 (IV)	36, 64	Cyclophosphamide 1000 mg/m^2 (IV)	36, 64
Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48, 52 – 55, 59 – 62	Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48, 52 – 55, 59 – 62
MTX + Cytarabine + Hydrocort (IT)	45, 59	MTX + Cytarabine + Hydrocort (IT)	45, 59
6-MP 60 mg/m^2 (PO)	36 – 63	6-MP 60 mg/m^2 (PO)	36 – 63
Consolidation Protocol M		Block 1	
Methotrexate 5000 mg/m^2 (IV)	8, 22, 36, 50	Vincristine 1.5 mg/m^2 (IV)	1, 6
MTX + Cytarabine + Hydrocort (IT)	8, 22, 36, 50	Methotrexate 5000 mg/m^2 (IV)	1
6-MP 25 mg/m^2 (PO)	1 – 56	Cytarabine 2000 mg/m^2 (IV)	5
		L-asparaginase 25000 IU/m^2 (IV)	6
		MTX + Cytarabine + Hydrocort (IT)	1
		Dexamethasone 20 mg/m^2 (PO)	1 – 5
		6-MP 100 mg/m^2 (PO)	1 – 5
		Block 2	
		Vincristine 1.5 mg/m^2 (IV)	1, 6
		Methotrexate 5000 mg/m^2 (IV)	1
		Cyclophosphamide 150 mg/m^2 (IV)	1 – 5
		L-asparaginase 25000 IU/m^2 (IV)	5
		Daunorubicin 50 mg/m^2 (IV)	5
		MTX + Cytarabine + Hydrocort (IT)	1
		Dexamethasone 20 mg/m^2 (PO)	1 – 5
		6-MP 100 mg/m^2 (PO)	1 – 5
		Block 3	
		Cytarabine 2000 mg/m^2 Q12H (IV)	1 – 2
		Etoposide 150 mg/m^2 (IV)	3 – 5
		L-asparaginase 25000 IU/m^2	5
		MTX + Cytarabine + Hydrocort (IT)	5
		Dexamethasone 20 mg/m^2 (PO)	1 – 5
Reinduction 2A		Reinduction 2A	
Doxorubicin 30 mg/m^2 (IV)	8, 15, 22, 29	Doxorubicin 30 mg/m^2 (IV)	8, 15, 22, 29
Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29	Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29
L-asparaginase 10000 IU/m^2 (SC)	8, 11, 15, 18	L-asparaginase 10000 IU/m^2 (SC)	8
Dexamethasone 10 mg/m^2 (PO) then taper	1 – 21	Dexamethasone 10 mg/m^2 (PO) then taper	1 – 21
MTX + Cytarabine + Hydrocort (IT)*	1, 8		

6-MP: 6-Mercaptopurine; IT: Intrathecal; IV: Intravenous; MTX: Methotrexate; PO: Per oral; RT: Radiotherapy; SC: Subcutaneous
*Patients with central nervous system involvement received these additional treatments.

Table 1. Hong Kong-Singapore (HK-SG) 97 Protocol (Cont'd)

Intermediate Risk	Day of Chemotherapy	High Risk	Day of Chemotherapy
Reinduction 2B		Reinduction 2B	
Cyclophosphamide 1000 mg/m^2 (IV)	36	Cyclophosphamide 1000 mg/m^2 (IV)	36
Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48	Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48
MTX + Cytarabine + Hydrocort (IT)	38, 45	MTX + Cytarabine + Hydrocort (IT)	38, 45
Cranial irradiation	36 – 50	6-MP 60 mg/m^2 (PO)	36 – 49
Maintenance (10 weekly for 24 months)		Interim maintenance	
Vincristine 1.5 mg/m^2 (IV)	57, 64	MTX + Cytarabine + Hydrocort (IT)	7, 14
Methotrexate 20 mg/m^2 (PO)	57	6-MP 50 mg/m^2 (PO)	1 – 28
MTX + Cytarabine + Hydrocort (IT)	1 – 70	Methotrexate 20 mg/m^2 (PO)	7, 14, 21, 28
6-MP 50 mg/m^2 (PO)	57 – 63	Cranial RT	8 – 22
Dexamethasone 6 mg/m^2 (PO)			
		Reinduction 3A	
		Doxorubicin 30 mg/m^2 (IV)	8, 15, 22, 29
		Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29
		L-asparaginase 10000 IU/m^2 (SC)	8
		Dexamethasone 10 mg/m^2 (PO) then taper	1 – 21
		Reinduction 3B	
		Cyclophosphamide 1000 mg/m^2 (IV)	36
		Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48
		MTX + Cytarabine + Hydrocort (IT)	38, 45
		6-MP 60 mg/m^2 (PO)	36 – 49
		Maintenance (10 weekly for 24 months)	
		Vincristine 1.5 mg/m^2 (IV)	57, 64
		6-MP 50 mg/m^2 (PO)	1 – 70
		Methotrexate 20 mg/m^2 (PO)	7, 14, 21, 28, 35, 42, 49, 56, 63, 70
		Dexamethasone 6 mg/m^2 (PO)	57 – 63

6-MP: 6-Mercaptopurine; IT: Intrathecal; IV: Intravenous; MTX: Methotrexate; PO: Per oral; RT: Radiotherapy; SC: Subcutaneous

*Patients with central nervous system involvement received these additional treatments.

to disease. One of these patients additionally had ON of the left shoulder, while 2 others also had multiple ON foci of the pelvic bones and sacrum. The fifth patient had ON of the right knee involving the femoral condyle, which required knee core decompression.

In 4 of the 5 patients, excluding the one who succumbed to disease, the first complaint of pain in the joint was reported during maintenance therapy. Subsequent magnetic resonance imaging (MRI) then revealed ON of the hip or knee. All total hip replacements, as well as the knee core decompression, were carried out after the completion of maintenance chemotherapy. All operations were performed successfully and without further complications. These 4 patients were still alive as of last follow-up, with a median survival of 70 months.

The last patient's ON of the hip was diagnosed incidentally on computerised tomography (CT) scans of the abdomen and pelvis which were done as part of investigations for sepsis.

Table 2 summarises these patients' osteonecrosis diagnosis and outcomes.

Discussion

Although a number of studies found the female gender to be a significant risk factor in developing ON,[1,2] this was not so for our cohort, where 80% of our patients with ON were male, from a cohort of 56% males and 44% females. Additionally, other studies performed in the United Kingdom and United States did not find such a correlation between ON incidence and the female gender.[10] As such, the impact of gender on ON pathogenesis remains controversial.

Dexamethasone has been increasingly used in ALL

Table 2. Patient Characteristics, ON Diagnosis and Outcomes

Patient No.	Gender	ALL Risk Stratification	Phase of Chemotherapy in Which ON Was Diagnosed	Site of Osteonecrosis	Surgical Procedures Performed	Survival (Months)
1	M	IR	Maintenance	Right knee	Right knee core decompression	32
2	M	IR	Maintenance	Bilateral hips, multiple foci in pelvic bones and sacrum	Bilateral THR	72
3	M	HR	Maintenance	Bilateral hips, left shoulder	Right THR	86
4	M	IR	Maintenance	Bilateral hips, multiple foci in pelvic bones and sacrum	Bilateral hip core decompression, left THR	67
5	F	IR	Salvage	Right hip	None	18

ALL: Acute lymphocytic leukaemia; F: Female; HR: High risk IR: Intermediate risk; M: Male; ON: Osteonecrosis; THR: Total hip replacement

protocols as it is more cytolytic compared to steroids.[11] However, dexamethasone is also more toxic to bone tissue,[12] resulting in a higher ON incidence. The Japanese Children's Cancer and Leukemia Study Group[7] found that ON was most prevalent in patients receiving only dexamethasone, suggesting that dexamethasone administration at any dose and in any treatment phase increases ON incidence.

A study done at St Jude Children's Research Hospital of 89 adolescents and young adults aged 15 to 18 years reported an ON incidence of 32.9%,[13] comparable to the 31.3% incidence within our study population. Total steroid doses in the St Jude study were lower than those used in our protocol. However, our incidence rate was also markedly higher than other reported incidences.[2,3] Comparing with the BFM 95 regime, which the HK-SG 97 was adapted from, our ON incidence is higher than the reported incidence of 11.1% among patients aged 14 to 18 treated with BFM 95.[1] This is despite the HK-SG 97 protocol having a similar total steroid dose for intermediate risk patients, and a lower total steroid dose for high risk patients, as compared to the BFM 95. This could possibly be due to the different racial heritage between the patients in the various studies, resulting in different genetic predispositions. It is also noted that our small sample size may give rise to a larger margin of random error, thus it would have been ideal to use a larger study cohort.

A few methods have been employed to reduce the risk of ON in adolescents and young adults with ALL. One of them is the practice of pre-emptive MRI of hips and knees soon after reinduction, in the hope that early detection would allow for therapeutic intervention such as steroid dose reduction.[13] This would also help in identifying asymptomatic ON. Additionally, another study found that alternate-week, instead of continuous administration of dexamethasone during delayed intensification therapy, lowered the incidence of ON.[14]

Conclusion

In view of our high ON incidence, we should strongly consider the strategies of early MRI screening and alternate-week dexamethasone therapy. Additionally, screening patients for relevant genetic polymorphisms in genes such as *ACP1* and *BMP7* could help identify those predisposed towards ON.

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