Abstract

Introduction: More than 80% of children with osteogenic sarcoma (OS) relapse and 35% to 40% of them die within the first 2 years after diagnosis due to relapse. We investigated the incidence, treatment modalities used and the outcome of patients with OS treated in Singapore. Materials and Methods: Patients with OS treated in Department of Paediatrics KK Women’s and Children’s Hospital (KKH) and National University Hospital (NUH) between January 1994 and June 2011 were reviewed. Chemotherapy was as per the European Osteosarcoma Intergroup (EOI) and as per the Memorial Sloan-Kettering Cancer Centre’s (MSKCC) T12 protocols. Overall and event-free (EFS) 5-year survivals were calculated using Kaplan-Meier analysis and Cox proportional hazards regression analysis. Results: Of 66 patients with OS, 19 (29%) of them presented with metastatic OS. The median age of diagnosis was 12.1 years with 5-year overall survival of 61.7% (95% CI, 48.1 to 75.3). The 5-year overall survival for those with non-metastatic and metastatic OS was 73.1% (95% CI, 58.1 to 88.1) and 34.7% (95% CI, 8.7 to 60.7, \( P = 0.007 \)) respectively. The 5-year overall survival for those treated as per the MSKCC T12 and EOI was 72.4% (95% CI, 52.6 to 92.2) and 54.3% (95% CI, 36.3 to 72.3, \( P = 0.087 \)) respectively. After controlling for confounding factors, patients with non-metastatic OS had higher 5-year EFS (HR, 0.228, 95% CI, 0.096 to 0.541, \( P = 0.001 \)) and overall survival (HR, 0.294, 95% CI, 0.121 to 0.713, \( P = 0.007 \)) compared to those with metastatic OS. Non-metastatic OS patients treated as per EOI regimen had lower 5-year EFS (HR, 2.397, 95% CI, 1.012 to 6.678, \( P = 0.047 \)) compared to those treated per MSKCC T12 regimen. Conclusion: Multidrug combination chemotherapy including high-dose methotrexate (HD-MTX) and a multidisciplinary team approach introduced in 2003 in Singapore is well tolerated and can be safely delivered. The survival benefit between the 2 regimens still needs to be explored.

Key words: Primary bone tumour, Singapore

Introduction

Osteogenic sarcoma (OS) is a primary malignant tumour of the bone, derived from primitive bone-forming mesenchyme and characterised by the production of osteoid tissue or immature bone by the malignant proliferating spindle cell stroma.1-2 Although primary bone tumours are rare in childhood, they are the sixth most common malignant neoplasms in children; in adolescents and young adults, they are the fourth most common malignant neoplasms, exceeded only by leukaemia, lymphomas and brain tumours.

There are 600 new cases per year reported in the United States but it occurs at a much lesser rate in Singapore. Its incidence rates among individuals under 24 years were 3.9 per million in men and women in Singapore. A Singapore Cancer Registry report by Shanmugaratnam K et al cites the incidence of OS over a 20-year period in Singapore as 20 cases per year.4 Since the introduction of multidrug regimen in the late 1970s, survival from localised OS elsewhere in the world was estimated at 60% to 78%.5-11 More than 80% of patients...
diagnosed with a primary, localised OS develop recurrent disease primarily in the lungs within the first 2 years after diagnosis. These patients subsequently succumbed to the disease. For approximately 30% of those who presented with pulmonary metastatic disease at the time of initial diagnosis, survival remains dismal at about 20%. Prior reports revealed that more than 95% of those who died had lung metastasis as indicated by autopsy at the time of death. 1,5 Although there is one report from Singapore on the survival experience with limb salvage emphasising the use of vascularised bone grafts and autoclaved tumour bone, we are not aware of any published studies on the various chemotherapy treatments given and the long-term outcomes for these young patients. 12 The current study was undertaken to report our experience on the clinical characteristics and survival outcome of these young patients with osteosarcoma treated in 2 major public hospitals, the KK Women and Children’s Hospital (KKH) and the National University Hospital (NUH), Singapore pre- and post-multidrug regimen with high-dose methotrexate (HD-MTX).

Materials and Methods

Patients

A comprehensive list of patients who presented to the Department of Paediatrics, KKH and the Departments of Paediatrics, Hand and Reconstructive Microsurgery, and Orthopaedics, NUH with newly diagnosed, high-grade OS was generated. The detailed medical record of each patient was thoroughly reviewed. Inclusion was restricted to patients first seen in KKH and NUH between January 1994 and October 2011. Every attempt was made to include all patients seen during the study period. The former date was chosen arbitrarily as a date by which the earliest KKH and NUH census (1994 onwards) recorded the first patient diagnosed with OS. The latter date was chosen to allow adequate time for follow-up at the time of the analysis. There were 72 patients with primary OS seen and treated in KKH and NUH during the study period. Patients who were seen only for an initial consultation and were lost to follow-up or patients whose medical records were not available (n = 5) and 1 patient whose histology review resulted in liposarcoma, were excluded in this analysis. Analysis is based on the 66 remaining patients.

Treatment

All patients received chemotherapy and surgery for the treatment of their OS. During the time period from January 1994 to June 2006 for the treatment of primary OS was also according to the EOI regimen. The EOI protocol consisted of 2-drug combination chemotherapy and surgery totalling approximately 24 weeks with some variations in the actual treatment period. Chemotherapy agents included a combination of cisplatin (100 mg/m²) given intravenously over 4 hours and doxorubicin (75 mg/m²) with continuous infusion given intravenously over 72 hours every 3 to 4 weeks. Surgery, either limb salvage or amputation at the discretion of the treating surgeon, was followed by 2 to 3 cycles of adjuvant chemotherapy. In NUH, from April 2003 onwards, the chemotherapy protocol used was adapted from the Memorial Sloan-Kettering Cancer Centre’s (MSKCC) T12 regimen and the Children’s Oncology Group (COG) regimen. 6,10 Multi-agent chemotherapy per cycle consisted of a combination of cisplatin (120 mg/m²) given intravenously over 4 hours with doxorubicin (75 mg/m²) given intravenously over 72 hours via continuous infusion; HD-MTX (12 g/m²) was given intravenously over 4 hours with folic acid (10 mg) given intravenously every 6 hours, first dose at hour 24 from the start of methotrexate (MTX); and ifosfamide (1.8 g/m²) given intravenously over 1 hour for 5 days with etoposide (100 mg/m²) given intravenously over 1 hour for 5 days. The treatment spanned over approximately 40 weeks with slight variation in the time required to complete the courses (Table 1). Surgery for all patients consisted of either limb salvage or amputation at the discretion of the treating surgeon and the team. Limb salvage surgical procedures at NUH were performed by using autoclaved tumour bone with vascularised bone graft or cadaver allograft bone as described previously, in addition to customised prostheses. 12 Patients with pulmonary metastatic disease underwent thoracotomies either immediately after definitive surgery of the primary tumour or at the end of their chemotherapy treatment. Treatment of subsequent relapses consisted of various chemotherapy regimens alone or surgery with or without additional individualised chemotherapy at both the centres. In some cases, high doses of radiation therapy were used.

Statistical Analysis

All analyses were performed using IBM SPSS 19.0. Descriptive statistics for quantitative variables were presented as median (range) and frequency (%) for qualitative variables. Adverse event-free survival (EFS) was defined as the endpoint in this study. This was defined as the time of entry into the study or time at diagnosis to the disease progression, occurrence of a metastatic disease, death from non-disease causes, development of a second malignant neoplasm, or last follow-up. The 5-year disease-free and overall survivals were calculated using
the method of Kaplan-Meier analysis. Cox proportional hazards regression model was performed to compare the disease-free and overall survivals adjusting for metastatic, non-metastatic disease and chemotherapy regimens. Statistical significance was set at $P < 0.05$.

**Results**

**Patient Characteristics**

Seventy-two patients were identified with a diagnosis of primary high-grade OS during the study period from January 1994 to October 2011. Six patients were excluded in this analysis as discussed above. Of the remaining 66 patients, the median age at diagnosis of primary OS was 12.1 years (range, 5.2 to 19.8 years), 26 patients were female (29%) and 40 were male (61%). The median follow-up for the entire cohort was 3.1 years (range, 0.3 to 13.3 years). The distributions of the initial site of OS were as follows: femur in 39 (59%) patients (31 distal), tibia in 15 (23%) patients, humerus in 9 patients (14%), 1 case each of clavicle and thoracic vertebrae, and the site of primary tumour was unknown in 1 patient. Only 1 patient presented with primary OS in the axial skeleton, in the thoracic vertebrae without any pulmonary involvement. Forty-seven (72%) patients presented with localised non-metastatic primary OS without any detectable pulmonary metastasis on imaging by chest x-ray (CXR) and/or computerised tomography (CT) scan. Of the 19 patients who presented with metastatic OS at diagnosis, 16 were to the lungs (8 = bilateral), 1 to multiple bones (lumbar L2-3 and ribs), 1 to scapula, and 1 patient presented with skip metastasis along the femur. The patient and tumour characteristics of all patients with OS are shown in Table 2.

**Surgery**

In patients who received chemotherapy as per the EOI protocol, 2 to 3 courses of neoadjuvant chemotherapy, every 3 to 4 weeks were delivered prior to undergoing surgical resection of the primary tumour. For those treated as per the MSKCC T12 regimen, surgery was performed at approximately 10 weeks from the start of chemotherapy. Sixteen (24%) patients underwent amputation as the surgical procedure for local control. Two patients did not have any surgeries for their primary tumours, whilst 1 patient’s local control procedure mode was unknown. The latter patient died of disease at 1.4 years from diagnosis. However, this patient presented with skip lesions at the time of initial diagnosis and underwent a limb salvage procedure against the treating surgeon’s advice.
Biologic Prognostic Factors

Of 66 patients, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) values at diagnosis were available for 31 (51%) of them. Our laboratory’s reference normal ranges for LDH and ALP are 250–580 U/L and 40–130 U/L respectively. Six patients presented with LDH levels of more than 1000 U/L whilst 8 presented with levels more than the normal but less than 1000 U/L. Of the 14 patients who presented with higher than the upper limit of normal levels of LDH and ALP, 7 were alive and 5 were dead of the disease. Huvos histological necrosis grading was not available in 22 patients. Huvos histological grading was defined as grade 1 with necrosis ≤50%; grade 2 with necrosis >50% <90%; grade 3 with necrosis >90% ≤99%; and grade 4 with necrosis of 100%.1 Huvos histological necrosis grading following preoperative chemotherapy was available for 44 of 66 patients who received neoadjuvant chemotherapy before definitive surgery for their primary OS (Table 3). Of the 44 patients whose tumour histological necrosis was available, 14 of 28 patients’ tumours with grade 1 to 2 and 10 of 16 patients’ tumours with grade 3 to 4 were alive with no evidence of disease.

Relapsed Patients

Salvage therapy for relapsed patients consisted of surgery with or without additional individualised chemotherapy. Of the 4 patients who were alive with no evidence of disease with relapsed OS to the lung, salvage therapy consisted of thoracotomy plus a combination of the following: ifosfamide (3 g/m²/day x 5 days) and muramyl tripeptide (MTP) (Patient 15); HD-MTX (12 g/m²/day) and ifosfamide (1.8 g/m²/
day x 5 days) (Patient 19); and MTX (8 g/m²); ifosfamide (1.8 g/m² x 5 days), etoposide (100 mg/m²/day x 5 days), cisplatin (120 mg/m²) and doxorubicin in 1 patient (Patient 21) (Table 3).

### Outcome

The 5-year EFS and overall survival for the cohort were 57.7% (95% CI, 43.9 to 71.5) and 61.7% (95% CI, 48.1 to 75.3) respectively (Figs. 1, 2). The 5-year EFS for those with non-metastatic OS was 69.3% (95% CI, 54.5 to 84.1), while for those with metastasis at diagnosis was 14.1% (95% CI, 0.0 to 38.1), \( P = 0.001 \) (Fig. 3). The 5-year overall survival for those with non-metastatic OS was 73.1% (95% CI, 58.1 to 88.1) while for those with metastasis at diagnosis was 14.1% (95% CI, 0.0 to 38.1), \( P = 0.001 \) (Fig. 3). The 5-year overall survival for those with non-metastatic OS was 73.1% (95% CI, 58.1 to 88.1) while for those with metastasis at diagnosis was 14.1% (95% CI, 0.0 to 38.1), \( P = 0.001 \) (Fig. 3). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the EOI regimen (Fig. 5). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the MSKCC T12 regimen (Fig. 5). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the MSKCC T12 regimen (Fig. 5). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the MSKCC T12 regimen (Fig. 5). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the MSKCC T12 regimen (Fig. 5). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the MSKCC T12 regimen (Fig. 5).

The 5-year EFS was 62.9% (95% CI, 41.9 to 83.9) per MSKCC T12 and 50.4% (95% CI, 31.2 to 69.6), \( P = 0.171 \) for patients who were treated as per the EOI regimen (Fig. 5). The 5-year overall survival was 72.4% (95% CI, 52.6 to 92.2) for patients who were treated as per the MSKCC T12 protocol versus 54.3% (95% CI, 36.3 to 72.3) \( P = 0.087 \) (Fig. 6). However, they were not statistically significant even though MSKCC T12 protocol appeared to have longer time to occur to events.

After controlling for potential confounding factors, when Cox proportional hazards regression model was applied, patients with non-metastatic OS had higher 5-year EFS (HR, 0.228, 95% CI, 0.096 to 0.541, \( P = 0.001 \)) as compared to those with metastatic OS. Patients treated as per EOI regimen had lower 5-year EFS (i.e. shorter time to have event) (HR, 2.397, 95% CI, 1.012 to 6.678, \( P = 0.047 \)) as compared to those treated as per the MSKCC T12 regimen (Fig. 7). In Cox regression model, patients with non-metastatic OS had higher 5-year overall survival (HR, 0.294, 95% CI, 0.121 to 0.713, \( P = 0.007 \)) as compared to those with metastatic OS (Fig. 7). However, chemotherapy regimens for MSKCC T12 versus EOI for 5-year overall survival were no longer statistically significant in the model (HR, 2.588, 95% CI, 0.987 to 6.782, \( P = 0.053 \)).

At the time of the analysis, median follow-up for the entire cohort from the time of diagnosis was 3.1 years (range, 0.3 to 13.3 years). Twenty-three (35%) were dead of disease. Forty-one (62%) patients were alive of which 36 (55%) were alive with no evidence of disease and 5 (7%) were alive with disease.

### Table 3: Patient and Tumor Characteristics of 21 Patients with Progressive or Relapsed Disease

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Primary Site</th>
<th>Metastatic Site</th>
<th>Relapse Site</th>
<th>Therapy 1/2nd Relapse</th>
<th>Type of Surgery</th>
<th>Huvos Grade</th>
<th>Dx-FU (Years)</th>
<th>Dx-R1 (Years)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>14.8/F</td>
<td>Femur</td>
<td>Lung</td>
<td>Lungs</td>
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<td>AKA</td>
<td>II</td>
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<td>0.5</td>
<td>DOD</td>
</tr>
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<td>EOI</td>
<td>AKA</td>
<td>I</td>
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<td>0.6</td>
<td>DOD</td>
</tr>
<tr>
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<td>Lungs, B</td>
<td>EOI</td>
<td>AKA</td>
<td>NOS</td>
<td>0.9</td>
<td>0.5</td>
<td>DOD</td>
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<td>EOI</td>
<td>Salvage</td>
<td>III</td>
<td>1.6</td>
<td>1.1</td>
<td>DOD</td>
</tr>
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<td>AMP</td>
<td>I</td>
<td>1.7</td>
<td>1.5</td>
<td>DOD</td>
</tr>
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<td>Lungs</td>
<td>EOI</td>
<td>AKA</td>
<td>NOS</td>
<td>1.8</td>
<td>0.3</td>
<td>DOD</td>
</tr>
<tr>
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<td>Thigh, L</td>
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<td>Salvage</td>
<td>I</td>
<td>1.8</td>
<td>1.8</td>
<td>DOD</td>
</tr>
<tr>
<td>8.</td>
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<td>Lungs, Humerus</td>
<td>EOI</td>
<td>Salvage</td>
<td>NOS</td>
<td>2.1</td>
<td>1.1</td>
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<tr>
<td>9.</td>
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<td>2.3</td>
<td>0.9</td>
<td>DOD</td>
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<td>T12</td>
<td>Salvage</td>
<td>III</td>
<td>2.6</td>
<td>0.6</td>
<td>DOD</td>
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<td>Lungs, B</td>
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<td>1.0</td>
<td>DOD</td>
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<td>B, Lungs</td>
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<td>1.9</td>
<td>DOD</td>
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<td>Salvage</td>
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<td>1.8</td>
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<td>Salvage</td>
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<td>1.3</td>
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</table>

ANED: Alive no evidence of disease; AKA: Above knee amputation; AMP: Amputation; AWD: Alive with disease; B: Bilateral; D: Distal; DOD: Dead of disease; Dx: Diagnosis; Dx-FU: Time diagnosis to follow up; Dx-R1: Time diagnosis to relapse; EOI: European Osteosarcoma Intergroup (cisplatin, doxorubicin); F: Female; M: Male; NOS: Not otherwise specified; P: Proximal; T12: High-dose methotrexate, cisplatin, doxorubicin, ifosfamide, etoposide; 1/: Primary tumour
Fig. 1. Graph showing the 5-year event-free survival in patients with osteogenic sarcoma (n = 66).

Fig. 2. Graph showing the 5-year overall survival in patients with osteogenic sarcoma (n = 66).

Fig. 3. Graph showing comparison of the 5-year event-free survival between non-metastatic versus metastatic osteogenic sarcoma in children patients.

Fig. 4. Graph showing comparison of the 5-year overall survival between non-metastatic versus metastatic osteogenic sarcoma in children patients.

Fig. 5. Graph showing comparison of the 5-year event-free survival by chemotherapy EOI versus T12 in children with osteogenic sarcoma.

Fig. 6. Graph showing comparison of the 5-year overall survival by chemotherapy EOI versus T12 in children with osteogenic sarcoma.
were alive with disease. One patient died of secondary leukaemia. This patient had thyroid carcinoma followed by OS and later succumbed to her third malignancy, leukaemia which occurred 4 years after completion of treatment of her OS. Of the 19 patients who presented with metastatic disease at diagnosis, 11 were dead of disease, 4 were alive with no evidence of disease, and 3 were alive with disease at the time of analysis. Twenty-one (32%) of 66 patients relapsed or had progressive disease at a median of 0.9 years (range, 0.3 to 2.5 years). All except 3 were relapses to the lung. Three patients had local recurrence after limb salvage procedure and 1 relapsed locally after amputation of the primary tumour in the humerus (Table 3). This latter patient's tumour achieved a grade 1 histological necrosis (Patient 20). One patient relapsed locally in the femur at 1.8 years from the initial diagnosis (Patient 7). This patient presented with skip metastasis at diagnosis and underwent a limb salvage procedure at the parents' request against the surgeon's advice, with positive margins at the time of definitive surgery. Four of the 21 relapsed patients were alive with no evidence of disease at the time of analysis from 3.9 to 13.3 years from diagnosis with interval from diagnosis of primary to time of development of relapsed OS between 0.7 to 1.8 years.

Discussion

Survival from primary localised OS elsewhere in the world is estimated at 60% to 78% at 5 years.6-11,13 We describe here the patient and tumour characteristics in children and young adults diagnosed with OS and demonstrate an improvement in survival when a multidrug regimen incorporating HD-MTX was instituted in 2003.

OS fortunately is a relatively rare cancer in our Southeast Asian children and young adults.3,4,12 The most common site of presentation of the primary tumour in our series was the distal femur at 59% similar to that reported elsewhere in the world. There was a slight male predominance occurrence with a median age of presentation at 12.1 years. The younger age of presentation in our series may likely be a consequence of our analysis which was restricted to the 2 major paediatric hospitals where the upper age limit for paediatric patients is 15 years. However, there are similar reports of younger age of presentation in Asian/Pacific Islanders.4 Seventy-seven percent of the patients were of Chinese ethnicity, which represented the majority of the population in Singapore. The remainder of the population consists of the Malays and the Indians at a lesser percentage which was also similar to the ethnic distribution of the disease. We also found in our series, similar to elsewhere in the world, that approximately one-third of the patients presented with evidence of pulmonary metastatic disease on computed tomography (CT) scan at the time of initial diagnosis.

Serum prognostic factors ALP and LDH levels were only routinely obtained at the time of diagnosis in 31 patients. Of the 14 with high levels of these biological enzymes markers, only 5 were alive. Although our numbers are too small to make a concrete conclusion, as previously reported in larger series, there was an inverse relationship between survival and the level of ALP and LDH.7,8 We now routinely obtain ALP and LDH at the time of diagnosis and follow-up serially. Huvos histological necrosis was also not consistently and routinely reported in all our patients. Although we were limited by the incompleteness of histological grading information for all our patients’ tumours, a higher tumour necrosis grade correlated with a better survival. However, in resource limited countries, efforts may be better allocated towards combating treatment abandonment and supportive care.

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There were a total of 3 local relapses in our cohort, 2 of whom underwent limb salvage procedures for their primary tumour extirpation. The limb salvage technique in NUH has long been based on the biological technique, with the use of vascularised bone grafts in combination with autoclaved tumour bone, details of which were described previously by Pho et al.12 In our analysis, the use of vascularised bone grafts in combination with autoclaved tumour bone did not appear to contribute to local recurrence in this small cohort of patients. This technique has also resolved the issue of limited resources in the region and the financial hardships which families face with high cost of customised prosthesis which are not covered by insurance or subsidies. Present analysis also revealed 21 patients who relapsed at a median of 0.9 years (range, 0.3 to 3.5 years) from the diagnosis of the primary tumour. There was little difference between the relapse rates and the site of relapse (lungs, in the majority of the patients) when patients who underwent amputation and limb salvage procedures were compared. However, the numbers were too small to detect whether there is a true significant difference.

In Singapore, for many years, the EFS and overall survival for patients with localised OS have been extremely poor at 40%. Elsewhere in the world, since the 1990s, survival rates for localised OS have plateaued in the range of 70% since the introduction of multidrug regimens incorporating HD-MTX. Modern management for children and young adults with OS has evolved mainly due to: multi-agent chemotherapy; better diagnostic imaging with multiplanar CT, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans; aggressive surgery with advanced surgical techniques; and excellent supportive care (antibiotics, nutrition, anaesthesia, biomedical engineering, and rehabilitation). Radiation therapy can be considered if surgery is not an option in selected cases such as vertebral column, brain, and pelvis. However, doses of more than 50-70 Gy must be given in conjunction with aggressive chemotherapy.15 Many centres also use irradiation as an additional palliative treatment. In Singapore multi-agent therapy based on MSKCC T12 regimen with HD-MTX was introduced only in the mid-2000s. The dose of cisplatin given in each course was increased to 120 mg/m²/cycle (previous dosing at 100 mg/m²/cycle) given over 4-hour infusion on 2 separate days. Although Ferrari et al in their randomised trial reported that the addition of ifosfamide onto the cisplatin/doxorubicin/MTX backbone did not improve survival outcome, our regimen incorporated ifosfamide and etoposide into the adjuvant phase.16 The promising role of ifosfamide combined with etoposide in OS was demonstrated initially by Miser et al and Gentet et al in separate studies in relapsed OS patients.17,18 This combination was later studied in a larger trial conducted by the Paediatric Oncology Group (POG) revealing 28 responses out of 39 newly diagnosed metastatic OS patients.19

This multidrug regimen together with advances in technology and excellent supportive care have allowed us to achieve improved survival rates of up to 70% reaching close to the world standards, for our young patients. It is important to note that there was no treatment-related toxic deaths throughout both the EOI and the T12 regimen eras. All patients succumbed to the disease. Hence, it is unlikely that this marginal higher survival was contributed in part by improved supportive care during the 2 treatments. The improved supportive care in the year 2000 onwards did indeed permitted safe delivery of multidrug intensive chemotherapy regimens such as T12. Albeit more intensive chemotherapy and a higher haematologic toxicity, this improved survival was clinically significant.

The field of paediatric oncology is evolving rapidly. It is in our best interest for the children to keep up-to-date with the current scientific discoveries, clinical trials results, and to practise best evidence-based medicine. Cure for children diagnosed with OS is possible when basic principles of therapy are applied. The key is to develop a committed and dedicated multidisciplinary team consisting of musculoskeletal oncology orthopedic surgeons, paediatric oncological surgeons, allied health members, and parents with clear goals. Secondly, we must all understand and agree that complete surgical extirpation of primary tumor is essential in both non-metastatic and metastatic disease. Despite two-thirds of patients succumbing to the disease, limb salvage rather than amputation, should be explored whenever feasible. Thirdly, effective systemic therapy must be delivered on strict schedule and without dose modification. It will be in our best interest to continue to visit whether a more intensive, stronger chemotherapy drug combinations and longer duration is in fact better than a simple two-drug regimen in a multicentre randomised controlled clinical trial settings. Lastly, the EFS and overall survival is not altered if macroscopic surgical resection is not done for metastatic and all clinically detectable disease, especially in those with pulmonary lesions. In conclusion, identifying and formulating optimal treatment strategies is complex and challenging for a child with both non-metastatic and metastatic OS. New drugs such as bisphosphonates, interferon, interleukin, and monoclonal antibodies have shown some encouraging results.20-22 Biology studies, especially in our unique setting may identify prognostic factors.

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