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Comparative Outcome on Tumor Necrosis of Two Versus Three Chemotherapeutic Regimens in Adult Osteosarcoma: Insight from Penang General Hospital

H Ahmad Munir[1], M Akmaludin[2], A Azid[3]

[1, 2, 3]Orthopaedic Oncology Unit, Department of Orthopaedic, Hospital Pulau Pinang, Malaysia
Email: *ammunir83[at]gmail.com*

Abstract: ***Standard treatment of osteosarcoma must include neoadjuvant chemotherapy followed by surgical resection and adjuvant chemotherapy. Preferred treatment as suggested by NCCN guideline include doxorubicin, cisplatin and methotrexate. Combination of cisplatin and methotrexate exerts significant toxicity and HDMTX require complex monitoring of the patients. OS - 99 study revealed that treatment containing doxorubicin, carboplatin, and ifosfamide produce comparable outcome to treatment containing HDMTX. This retrospective study compares the outcomes of tumor necrosis in adult osteosarcoma patients treated with either a two drug regimen doxorubicin and cisplatin or a three drug regimen doxorubicin, cisplatin, and ifosfamide at Penang General Hospital. The study spans from 2020 to 2024 and includes 16 patients with resectable osteosarcoma of the extremities. The results indicate no significant difference in tumour necrosis between the two regimens, with both achieving comparable outcomes. Given the similar efficacy, the two drug regimen may be preferable for older patients or those with comorbidities due to its lower toxicity.***

Keywords: osteosarcoma, chemotherapy, tumour necrosis, doxorubicin, ifosfamide

1. Introduction

Osteosarcoma is the most common malignant primary bone tumour. It is characterized by an osteoid or immature bone producing tumour with malignant mesenchymal cells. Peak incidence is in the second decade of life. It can generally be classified into low - grade and high - grade osteosarcoma. Before the usage of chemotherapy in 1970 survival rate of osteosarcoma was as low as 20% even if the tumour was resectable at presentation. [1] Since the introduction of multi modal chemotherapy (neo - adjuvant and adjuvant) and combination with good surgical resection survival rate has improved to about 70%. [1] Despite good response to chemotherapy, it exposed patient to many side effects as drugs used in the treatment exert significant toxicity. [2] Multiple studies have been done to look for the best outcome with less side effects. Our study is to share our experience in managing osteosarcoma in adult patients by comparing the use of combinations of two and three chemotherapy agents without the use of high - dose methotrexate (HDMTX). The purpose of this study is to evaluate and compare the effectiveness of two drug versus three drug chemotherapy regimens in achieving tumour necrosis in adult osteosarcoma patients, with the aim of identifying a treatment approach that balances efficacy and toxicity. The significant of this study is it contributes to the ongoing discussion regarding optimal chemotherapy regimens for osteosarcoma, particularly in adult patients where treatment choices are complicated by factors such as age and comorbidities.

2. Method

This is a retrospective study of osteosarcoma patients treated in Hospital Pulau Pinang from year 2020 until 2024. All patients were diagnosed as primary osteosarcoma treated by orthopaedic team and adult medical oncology team in our hospital. We included only patients who was treated with either two chemotherapeutic agents (doxorubicin and cisplatin) and three drugs (doxorubicin, cisplatin and ifosfamide). First group was treated between year 2020 until 2021 with two chemotherapeutic agents and second group was treated between 2022 and 2024 with three chemotherapeutic agents. All patients involved only extremities and were resectable at diagnosis. Total number of patients were 16 with 8 patients in each group. We looked at tumour necrosis rate according to HUVOS classification and divided it into good tumour necrosis (HUVOS grade III and IV) and poor tumour necrosis (HUVOS grade I and II). [3]

3. Results

Since the year 2020 until 2024 we had 16 patients that was treated in our hospital by our adult medical oncology team who meet the criteria. The two drug groups patients had treatment from year 2020 until 2021 and the three drugs group had treatment from 2022 until 2024.

Looking at age distribution the two drugs group had patients from the age of 19 until 59 - year - old with mean age is 32.7, while in three drugs group the age is from 16 until 45 - year - old with mean age is 24.6.

For gender, the two drugs group had balance number of male and female while in three drugs group had 5 males and 3 females.

All patients were osteosarcoma of extremities which were operable at diagnosis and limb salvage surgery were performed. Among 16 patients most common anatomical site involved was distal femur which were 7 patients, 4 proximal humerus, 2 proximal tibia, 1 total femur, 1 diaphyseal femur and 1 distal tibia.

All patients had R0 margin except 1 patient in three drugs group had R1 margin.

In our limited cohort, we found that both groups had the same number of good responders in terms of tumour necrosis which is only 37.5%.

Table 1: Two Drugs group

Patient	Age	Gender	Margin	HUVOS
A2	20	M	R0	H3 98%
B2	59	F	R0	H4 100%
C2	19	M	R0	H1 10%
D2	21	M	R0	H1 30%
E2	18	F	R0	H2 85%
F2	50	F	R0	H3 95%
G2	28	F	R0	H2 65%
H2	35	M	R0	H2 75%

Table 2: Three Drugs group

Patient	Age	Gender	Margin	Huvos
A3	19	M	R0	H4 100%
B3	17	M	R1	H2 55%
C3	26	F	R0	H3 95%
D3	19	F	R0	H2 40%
E3	26	F	R0	H2 70%
F3	16	M	R0	H2 55%
G3	45	M	R0	H3 97%
H3	29	M	R0	H2 85%

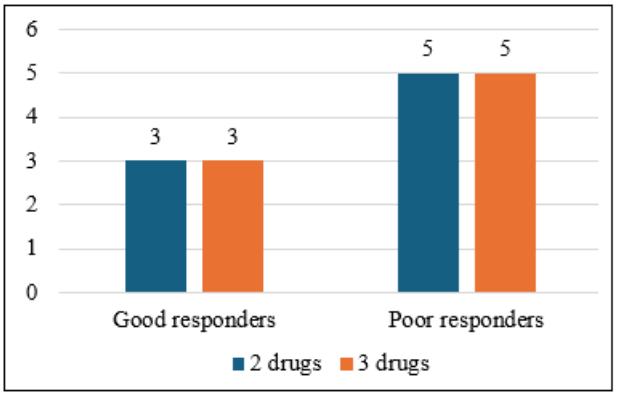

Figure 1: Tumor Necrosis

4. Discussion

Chemotherapy is an essential part of treatment in osteosarcoma. Its most important aim is to eliminate micro metastatic cells. It also reduces tumour size and solidify the tumour that ease surgical resection aiming for clear margin surgery. The rationale for neoadjuvant chemotherapy started from landmark study by Rosen et al from Memorial Sloan Kettering Cancer Centre in 1982. [1, 4] Their approach was confirmed by series of studies conducted at the Rizzoli Institute by Bacci et al using multimodal agent of high - dose methotrexate (HDMTX), doxorubicin and cisplatin (MAP) which improved overall survival greater than 60% and limb salvage to greater than 80%. [5, 6]

The current National Comprehensive Cancer Network (NCCN) guidelines for high - grade osteosarcoma include both doxorubicin and cisplatin as recommended first line of treatment or doxorubicin, cisplatin and high - dose methotrexate (MAP). [7] Other recommended regimens for primary neoadjuvant and adjuvant therapy include doxorubicin, cisplatin, ifosfamide, and HDMTX, as was used in the Rizzoli protocols. [6, 5]

It is well known that tumour respond to chemotherapy is the most significant prognostic factor in osteosarcoma. [8, 9] A good responder was defined as a necrosis higher than 90% or less than 10% of viable tumour post operatively using HUVOS classification. Even though some have argued that a good responder does not necessarily have a good overall survival, it is established that a poor responder has a worse overall survival. [10] Other factors which may affect tumour necrosis such as histologic subtype, tumour size, tumour location, age and gender however all these factors are non - modifiable. Based on this fact, many studies have been conducted to get the best results using multi drug combinations to treat osteosarcoma. It is a challenging task as chemotherapy drugs has its own toxic effect furthermore if it is used in combination which may cause serious adverse effects to patients.

In our centre previously our oncologist preferred to give only 2 drugs as in NCCN guideline, however the tumour response that we had was not satisfactory in compare with our paediatric group patients who received three drugs (MAP). After reviewing the outcomes of three drugs combination (MAP) of our patients treated by our paediatric oncology team and OS - 99 trial from St. Jude Children Research Hospital we decided to change the practice from two drugs to three drugs without methotrexate. We were able to avoid the toxicity of HDMTX in our adult patients yet able to give multi - agents as suggested by OS - 99 trial. Despite comparable outcome reported in OS - 99 trial our experience showed that no difference between two drugs and three drugs regime.

Doxorubicin may cause serious adverse effects as cardiotoxicity and bone marrow suppression. It may be reversible such as arrhythmia which may occur in 26% of patients, myopericarditis and left ventricular dysfunction. It may also cause irreversible cardiomyopathy which may occur a few months after end of treatment and up to 25 years. [11] High dose methotrexate is a potentially very toxic. It may cause bone marrow suppression, pulmonary toxicity, nephrotoxicity, haematological toxicity, and can increased risk of infections. [12] Its usage is often combined with few leucovorin rescue doses to treat methotrexate toxicity together with closed pharmacokinetic monitoring of the patient. [2] Common side effects for ifosfamide include hematuria which occur in 90% of patients. [13] Hematological side effects as anemia, leucopenia and thrombocytopenia occur in 30% - 50% of patients. [13] Metabolic acidosis may occur in 30% of patients and other less common side effects as encephalopathy and arrhythmia may be seen in 10% - 15% of patients. [13] On the other hand, cisplatin may cause irreversible renal impairment and ototoxicity. [14, 15, 16] It is also one of the most emetogenic chemotherapy agents. [13]

In older patients especially with multi comorbidities, multi agent chemotherapy must be carefully given due to their tolerance to the drugs is limited in compare with paediatric patient. [17] Many centres preferred to give two drugs without HDMTX to their adult age groups of osteosarcoma patients rather than three drugs as HDMTX is a very toxic drug as

mentioned before which require rigorous pharmacokinetic monitoring and rescue with leucovorin dose - adjusted to MTX levels. Furthermore, some centres are not able to provide such monitoring to patients which make chemotherapeutic regime without MTX greatly beneficial.

To date there is still no targeted therapy or immunotherapy can effectively treat osteosarcoma. However, the understanding of osteosarcoma is gradually increasing through molecular analysis technique. [18] We hope this advancement will help in future clinical trials looking at new treatment for osteosarcoma.

5. Conclusion

This study concludes that the two drug regimen of doxorubicin and cisplatin is as effective as the three drug regimen with ifosfamide in achieving tumour necrosis in adult osteosarcoma patients. Given the comparable outcomes and the potential for reduced toxicity, the two drug regimen may be preferable, especially for older patients or those with comorbidities. Further studies with larger sample sizes are recommended to confirm these findings and explore the potential benefits of adding ifosfamide to the treatment regimen.

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Author Profile

Ahmad Munir Hashim received MBBcH from Ain Shams University, Cairo in 2009 and Master in Orthopaedic Surgery from IIUM, Malaysia in 2019. Currently I am Orthopaedic Oncology fellow in Ministry of Health Malaysia and practicing in Hospital Pulau Pinang, Malaysia. I am involved in clinical works, teaching and research as well as participating in conferences and seminars.