

Effectiveness of mifamurtide in addition to standard chemotherapy for high-grade osteosarcoma: a systematic review

A thesis submitted by

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Table of Contents

ABBREVIATIONS	IV
ABSTRACT	VII
DECLARATION.....	X
ACKNOWLEDGMENT	XI
CHAPTER 1: INTRODUCTION	1
Thesis structure.....	1
Overview of chapter 1.....	1
Contextual overview on osteosarcoma	2
Basic bone structure and function	2
Cancer and types of bone cancer.....	2
Classification and histomorphology of osteosarcoma	3
Osteosarcoma staging system and statistics	4
Osteosarcoma diagnosis	4
Signs and symptoms of osteosarcoma.....	5
Physical examination.....	5
Imaging tests	5
Biopsy.....	7
Laboratory tests	7
Risk factors for osteosarcoma.....	7
Age	8
Gender.....	8
History of radiation exposure	8
Inherited cancer syndromes and bone diseases.....	8
Current treatment regimen for high-grade osteosarcoma.....	9
Chemotherapy.....	9
Surgery	9
Innovative therapeutic approaches	10
Immune stimulatory agents	10
Mifamurtide drug history.....	10
The molecule and its formulation	10
Mechanism of action.....	11
Dosage and administration of mifamurtide.....	11
CHAPTER 2: METHODOLOGY	13
Evidence-based healthcare (EBHC).....	13
The JBI approach to EBHC	14
Evidence synthesis	15
The systematic review.....	16
Levels of evidence and the grading of recommendations	17
The need for conducting a review	18
CHAPTER 3: SYSTEMATIC REVIEW METHODS	20
Inclusion criteria.....	20
Types of participants.....	20
Types of interventions and comparator.....	20

Types of outcomes and outcome measures	20
Types of studies.....	21
Review methods.....	21
Search strategy.....	21
Assessment of methodological quality	22
Data extraction.....	22
Data synthesis	22
CHAPTER 4: RESULTS.....	23
Description of search results and study selection	23
Description of included studies.....	25
Randomised controlled trial.....	25
Quasi-experimental before and after study.....	26
Methodological quality	26
Narrative results.....	28
Primary outcomes	28
Secondary outcomes.....	34
CHAPTER 5: DISCUSSION AND CONCLUSION	37
Overview of findings	37
Effectiveness of mifamurtide in addition to standard chemotherapy on EFS for high-grade osteosarcoma.....	37
Effectiveness of mifamurtide in addition to standard chemotherapy on overall survival for high-grade osteosarcoma.....	37
Recurrence of osteosarcoma	38
Effectiveness of mifamurtide in addition to standard chemotherapy on mifamurtide-related adverse events and HRQoL for high-grade osteosarcoma.....	38
Limitations of the review	38
Conclusion.....	40
Implications for practice	40
Implications for research	43
CONFLICT OF INTEREST	44
REFERENCES	45
APPENDICES	50
Appendix I: JBI Levels of evidence	50
Appendix II: New JBI Grades of Recommendation	51
Appendix III: Search strategy	52
Appendix IV: Appraisal instrument	59
Appendix V: Data extraction instrument	60
Appendix VI: Studies excluded after review of full text.....	62
Appendix VII: Characteristics of included studies.....	72

List of tables

Table 1: Enneking Staging System ²¹	4
Table 2: Application of GRADE quality of evidence in the GRADE approach	18
Table 3: Results of critical appraisal of included randomised controlled trial/pseudo-randomised trial	27
Table 4: Five-year EFS in metastatic osteosarcoma patients according to treatment regimen (Chou et al. ¹).....	29
Table 5: Four-year and six-year EFS in non-metastatic osteosarcoma patients according to treatment regimen (Meyers et al. ²)	30
Table 6: PFS in pulmonary metastatic osteosarcoma patients according to treatment regimen (Kleinerman et al. ³).....	30
Table 7: Five-year overall survival in metastatic osteosarcoma patients according to treatment regimen (Chou et al. ¹)	32
Table 8: Four-year and six-year overall survival in non-metastatic osteosarcoma patients according to treatment regimen (Meyers et al. ²)	33
Table 9: Survival after relapse in pulmonary metastatic and/or relapsed osteosarcoma patients according to treatment regimen (Kleinerman et al. ³).....	33
Table 10: Mifamurtide-related adverse events in metastatic osteosarcoma patients according to treatment regimen (Chou et al. 2009 ¹).....	35
Table 11: Summary of Findings	42

List of figures

Figure 1: The JBI Model ⁶⁵	14
Figure 2: Flow chart for identification of studies for inclusion and exclusion	24

ABBREVIATIONS

ARTG – Australian Register of Therapeutic Goods

BLM – Bloom syndrome

CCG – Children’s Cancer Group

COG – Children’s Oncology Group

CI – Confidence Interval

CT – Computed tomography

DNA – Deoxyribonucleic acid

EBHC – Evidence-based healthcare

EFS – Event-free survival

EMA – European Medicines Agency

FAME – Feasibility, Appropriateness, Meaningfulness and Effectiveness

FDA – Food and Drug Administration

GRADE – Grading of Recommendations, Assessment, Development and Evaluation

HDMTX – High-dose methotrexate

HER2 – Human epidermal growth receptor-2

HRQoL – Health-related quality of life

HR – Hazard ratio

IGF1R – Insulin-like growth factor receptor 1

IL-1 – Interleukin 1

IL-6 – Interleukin 6

IL-8 – Interleukin 8

IRAEs – Infusion-related adverse events

JBI – Joanna Briggs Institute

JBI-SUMARI – Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information

JBIMASARI – Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument

JBISRIR – Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports

LDH – Lactate dehydrogenase

L-MTP-PE – Liposomal muramyl tripeptide phosphatidylethanolamine

mCi – Millicurie

MDACC – MD Anderson Cancer Center

MRI – Magnetic resonance imaging

MeSH – Medical Subject Headings

MTP – Muramyl tripeptide

MTP-PE – Muramyl tripeptide phosphatidylethanolamine

MDP – Muramyl dipeptide

MTD – Maximum tolerated dose

NOD2 – Nucleotide-binding oligomerisation domain-containing protein 2

NaCl – Sodium Chloride

NCCN – National Comprehensive Cancer Network

NCI – National Cancer Institute

NF – Nuclear factor

NPP – Named Patient Program

OR – Odd Ratio

PET – Positron emission tomography

PICO – Population, Intervention, Comparator and Outcomes

PFS – Progression-free survival

POG – Pediatric Oncology Group

pRb – Retinoblastoma protein

RecQ – Structurally-related DNA helicase

RECQL – gene encoding one member of a protein family called RecQ helicases

RNA – Ribonucleic acid

RCTs – Randomised controlled trials

RR – Relative risk

SPSS/PC+ - Statistical Package for the Social Sciences/PC+

TP3 – Therapeutic antibody administration

TGA – Therapeutic Goods Administration

TNF- α – Tumour necrosis factor-alpha

Tc99m MDP – technetium 99m methylene diphosphonate

WHO – World Health Organisation

WRN – Werner syndrome

ABSTRACT

Background

Osteosarcoma mostly occurs during the period of rapid bone growth in children and adolescents as high-grade osteosarcomas. Current treatment recommended for high-grade non-metastatic and metastatic and/or relapsed osteosarcoma involves neoadjuvant multiagent conventional chemotherapy, followed by surgical resection of macroscopically detected tumour and postoperative adjuvant chemotherapy. However, residual micrometastatic deposits that develop following surgery have shown resistance to postoperative/adjuvant chemotherapy. Therefore, there is a critical need for more effective and innovative therapeutic approaches such as immune stimulatory agents. The most extensively studied immune stimulatory agent in the treatment of osteosarcoma is mifamurtide. The aim of this systematic review was to identify and synthesise the evidence on the effectiveness of mifamurtide in addition to standard chemotherapy on survival outcomes.

Objectives

To present the best available evidence related to the treatment of high-grade non-metastatic and metastatic osteosarcoma with mifamurtide in addition to standard chemotherapy.

Inclusion criteria

Types of participants

All populations of patients, regardless of age, gender or ethnicity with high-grade, resectable, non-metastatic and metastatic osteosarcoma based on histological diagnosis.

Types of interventions and comparators

This review focused on intravenous infusion of either of the pharmaceutical formulations of mifamurtide (MTP-PE or L-MTP-PE) in addition to standard chemotherapy, and the comparator was chemotherapy alone.

Types of studies

This review considered any experimental study design including randomised controlled trials, non-randomised trials and quasi-experimental studies.

Types of outcomes

The primary outcomes of interest were event-free survival, overall survival and recurrence of osteosarcoma. Secondary outcomes that were considered included health-related quality of life and any mifamurtide-related adverse events.

Search strategy

A search for published and unpublished literature in the English language was undertaken (seven published literature databases, four unpublished literature databases, and three government agency and organisational websites). Studies published between 1990 to June 2016 were considered. A three-step strategy was developed using MeSH (Medical Subject Headings)

terminology and keywords to ensure that all relevant studies related to this review were included.

Methodological quality

The methodological quality of included studies was assessed by two reviewers, who appraised each study independently, using a standardised Joanna Briggs Institute (JBI) critical appraisal tool.

Data extraction

Data was extracted from the studies that were identified as meeting the criteria for methodological quality using the standard JBI data extraction tool.

Data synthesis

Due to the heterogeneity of populations and interventions and available studies, meta-analyses were not possible and results are presented in narrative form.

Results

Three papers outlining two studies involving 802 patients evaluated the effectiveness of mifamurtide in addition to chemotherapy. Results indicated no significant difference in event-free survival between the addition of mifamurtide to standard chemotherapy regimens and chemotherapy alone, both in non-metastatic and metastatic osteosarcoma patients. There was a significant difference in progression-free survival favouring the addition of mifamurtide in pulmonary metastatic and/or relapsed osteosarcoma. There was no significant difference in overall survival between the addition of mifamurtide and chemotherapy alone in metastatic osteosarcoma; however there was a significant difference favouring the addition of mifamurtide in non-metastatic osteosarcoma patients. The addition of mifamurtide resulted in a significant difference in survival after relapse in pulmonary metastatic and/or relapsed osteosarcoma patients. Both studies reported on mifamurtide-related adverse events – the first was reported as toxicity which included haematological, hepatic, renal, gastrointestinal disorders, cardiac rhythm, nervous system disorders, ear disorders and others (infection, fever and performance status) in metastatic osteosarcoma patients. Results were similar across all combined treatment regimens. Although no statistical analysis was undertaken, the figures suggest there were no significant differences between the treatment regimens. In the other study, mifamurtide-related adverse events were reported as clinical toxic effects of mifamurtide in relapsed osteosarcoma, which included chills, fever and headache for the initial dose of mifamurtide, while for the subsequent doses of mifamurtide all patients reported toxicity as delayed fatigue.

Conclusions

The available evidence on the effectiveness of mifamurtide in addition to a standard chemotherapy regimen for the treatment of high-grade osteosarcoma is limited and therefore no definitive conclusions can be made.

Implication for practice

There is currently limited evidence to recommend or refute the addition of mifamurtide to the standard chemotherapy regimen for the treatment of high-grade osteosarcoma.

Implication for research

Additional high quality studies such as randomised controlled trials or quasi-experimental studies involving a larger sample size are required. Consistency in outcome measures is critical to facilitate comparison.

Cost-effectiveness studies of mifamurtide are required to inform choice from a societal perspective.

Keywords

Osteosarcoma, osteogenic sarcoma, mifamurtide, 'muramyl tripeptide phosphatidylethanolamine', 'muramyl tripeptide'.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Date:

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