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

A thesis submitted by

Rincy Jimmy

in partial fulfilment of the requirements for the degree of
Master of Clinical Science (MClinSc)

The Joanna Briggs Institute

Faculty of Health and Medical Sciences

The University of Adelaide

Australia

Table of Contents

List of tables

List of figures

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

JBI-MAStARI – 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.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Rincy Jimmy: ……..…….....

Date: ……

ACKNOWLEDGMENT

I acknowledge and thank the Joanna Briggs Institute for providing me with extended support to undertake the critical learning course work to enable me to commence the systematic review process.

A big thank you to my academic supervisors, both past and present, from the Joanna Briggs Institute: Dr Sarahlouise White, Dr Karolina Lisy and Dr Cindy Stern. I have learned so much from your expertise and many thanks for the considerate support and encouragement throughout the course.

I offer my appreciation to Dr. Catalin Tufanaru for statistical advice.

A special thank you is reserved for my husband and children who have encouraged me throughout, with pride and enthusiasm, to achieve this body of work, and who have allowed me the indulgence of time to complete it. Thank you to my parents, who have been motivational, and also friends, who have assisted my family in every way possible to enable me to indulge in this process.

Most importantly, being a member of Cancer Voices SA, and from a consumer perspective, I dedicate this work to Joby Joseph, my beloved brother, who lost the battle against osteosarcoma. A contributor and keeper of knowledge, not much was known to him as a consumer, but he remains my inspiration for continual learning.