Investigating chemotherapy adverse events: incidence, costs and consequences

Alison Pearce

Centre for Health Economics Research and Evaluation

Faculty of Business

University of Technology, Sydney

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Certificate of original authorship

I certify that the work in this thesis has not previously been submitted for a degree, nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Alison Pearce

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Abbreviations and shortened forms

ACAS	Australian Cancer Anaemia Survey
ACT	Australian Capital Territory
ADL	activities of daily living
AE	adverse event
AIC	Akaike's Information Criteria
ANC	absolute neutrophil count
APDC	Admitted Patient Data Collection (NSW)
AR-DRGs	Australian Refined Diagnosis Related Groups
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATC	Anatomical Therapeutic Chemical
BCCA	British Columbia Cancer Agency
bid	twice per day
CADTH	Canadian Agency for Drugs and Technology in Health
CCR	Central Cancer Registry (NSW)
CHeReL	Centre for Health Record Linkage
CI	confidence interval
CPT-11	irinotecan
CTCAE	Common Terminology Criteria for Adverse Events
DRG	diagnosis related group
DVA	Australian Government Department of Veterans' Affairs
ECAS	European Cancer Anaemia Survey
EDDC	Emergency Department Data Collection (NSW)
EMCaP	Economic Models for Cancer Protocols
EORTC	European Organisation for Research and Treatment of Cancer
EPO	erythropoietin
ESA	erythropoiesis stimulating agent
ESMO	European Society of Medical Oncology
FDA	US Food and Drug Administration
5-FU	5-fluorouracil
5-HT3RA	5-HT3 receptor antagonists
g/dL	grams per decilitre
GEE	generalised estimating equations
GLM	generalised linear modelling
GP	general practitioner
G-CSF	granulocyte colony-stimulating factor
Hb	haemoglobin
hrs	hours
ICER	incremental cost-effectiveness ratio

ICU	intensive care unit
IM	intramuscular
inpt	inpatient
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVT	intravenous therapy
lab.	Laboratory
MASCC	Multinational Association of Supportive Care in Cancer
max.	maximum
MBS	Medicare Benefits Schedule
MATES	Medicines Advice and Therapeutics Education Services
MeSH	medical subject heading
mg	milligram
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHCDC	National Hospital Cost Data Collection
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute of Health and Care Excellence
NS	not specified
NSCL	non-small-cell lung cancer
NSW	New South Wales
OOP	out-of-pocket
OLS	ordinary least squares
outpt	outpatient
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PICO	population / intervention / comparison / outcome
PLD	pegylated liposomal doxorubicin
PPN	unique patient identifier
QALY	quality adjusted life year
QIC	quasi-likelihood under the independence model criterion
QICu	simplified quasi-likelihood under the independence model criterion
RBC	red blood cell
RDI	relative dose intensity
RPBS	Repatriation Pharmaceutical Benefits Scheme
SA	sensitivity analysis
SC	Schwarz Criterion
SQ	subcutaneous

SESIAHS	South Eastern Sydney and Illawarra Area Health Service
TGA	Therapeutic Goods Administration
tid	three times per day
TTO	time trade-off
U	units
µg	microgram
UK	United Kingdom
US	United States
v.	versus

Abstract

Background: In Australia, economic evaluation is an important tool in prioritising healthcare spending. Adverse events of chemotherapy affect patients' physical health and quality of life; however, they are often excluded from chemotherapy economic evaluations. This thesis explores the incidence, costs and consequences of chemotherapy adverse events and the implications for cost-effectiveness.

Key Objectives:

1. Examine how adverse events are incorporated into models of chemotherapy cost-effectiveness.
2. Develop Australia-based models of costs and consequences of four common adverse events.
3. Estimate incidence of adverse events in clinical practice.
4. Estimate costs of adverse events in clinical practice.
5. Compare rates of adverse events in clinical practice with rates reported in clinical trials.

Methods: There are four components to this research. The first is a systematic review examining how adverse events are incorporated into existing models of chemotherapy cost-effectiveness (Objective 1). The second is the use of decision analytic modelling to develop models of the costs and consequences of diarrhoea, nausea/vomiting, anaemia and neutropoenia. These can then become standard components of future models of chemotherapy cost effectiveness (Objective 2). The third is the use of regression to estimate the incidence and costs of adverse events (Objectives 3 and 4) in an administrative dataset linked to routinely collected data on pharmaceutical and medical service use. Finally, an analysis of a prospective cohort of 482 individuals undergoing chemotherapy examines the frequency of adverse events (Objective 3) in comparison with those reported in clinical trials (Objective 5).

Results: The systematic review revealed that adverse events are not included in models of chemotherapy cost-effectiveness in any rigorous way. The models developed demonstrate that rigorous, systematic consideration of the key costs

and consequences of adverse events is possible, and provide a standard way to include adverse events in future models. Older or sicker individuals in the administrative dataset were more likely to experience adverse events, although incidence was low. Mean healthcare costs significantly increased with treatment for nausea, anaemia or neutropoenia but not diarrhoea. The prospective cohort study identified higher rates of adverse events than reported in clinical trials, with low-severity events particularly common.

Conclusions: In exploring the incidence, costs and consequences of chemotherapy adverse events, this thesis demonstrates that it is possible to model the key costs and consequences of chemotherapy adverse events, and that clinical practice data may reduce bias in these models. This is a significant contribution to determining true chemotherapy costs and consequences.