Project: Clinical Effectiveness of Treatment Options for Relapsed or Refractory Multiple Myeloma

Research Protocol

March 9, 2016
Version 1.0

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BACKGROUND, OBJECTIVES, AND RESEARCH QUESTIONS

Background

Multiple myeloma (MM) is a blood cancer in which the bone marrow produces an overabundance of malignant plasma cells that emerge into the bloodstream. Ultimately, the proliferation of plasma cells can cause bone damage, anemia, low white blood cell counts, and kidney failure.[1] Approximately 25,000 cases of MM are diagnosed in the U.S. annually, with three quarters of affected individuals over 70 years of age. There is no cure for multiple myeloma, but its progression can be relatively slow in many individuals, often involving multiple rounds of remission after treatment followed by a subsequent relapse. Recent advances in therapy have greatly improved the disease's prognosis. Nearly half of all patients will survive at least 5 years after diagnosis, and nearly 100,000 individuals are currently living with the disease in the U.S.[2] The costs of managing multiple myeloma are substantial, given the use of multiple therapies over the course of the disease. The cost of a single course of drug therapy has been estimated to range from $75,000 - $250,000 for patients with relapsed or refractory disease.[3] Many patients are also treated with a hematopoietic stem cell transplant early in the disease course, the costs of which can range from nearly $60,000 in uncomplicated cases to double this figure in cases with infectious complications or stomatitis.[4,5]

Over the past decade the treatment of MM in the U.S. has been anchored by two drugs, often given in combination with dexamethasone. The first of these drugs to enter use was the proteasome inhibitor bortezomib (Velcade®, Takeda Millenium) in 2003, followed by the immune modulator lenalidomide (Revlimid®, Celgene) in 2005. Other medications have more recently become available specifically for the treatment of relapsed or refractory disease, including the immune modulator pomalidomide (Pomalyst®, Celgene), proteasome inhibitors carfilzomib (Kyprolis®, Onyx) and ixazomib (Ninlaro®, Takeda), the monoclonal antibody daratumumab (Darzalex®, Janssen Biotech), the immunostimulatory antibody elotuzumab (Empliciti®, Bristol Myers-Squibb), and the histone deacetylase inhibitor panobinostat (Farydak®, Novartis Pharmaceuticals Corp.). There is uncertainty, however, regarding the comparative tradeoffs between effectiveness and toxicity of these therapies and their various combinations. Cost considerations have also increased along with the list prices and potential for multiple drug combinations in varying sequences. Thus there remains substantial uncertainty regarding how best to interpret and apply the available evidence to guide clinical practice and insurance coverage policies.

Overview

This project will evaluate the health and economic outcomes of multiple treatment regimens for relapsed or refractory multiple myeloma. Evidence will be culled from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated as necessary. We will not restrict studies according to clinical development phase, comparators, or study setting; however, we will limit our review to those studies that match FDA-

approved indications for use and dosing for the regimens of interest, as well as those that capture the key outcomes. Studies comparing one of the listed regimens for this assessment to an investigational regimen without a current FDA indication will be excluded. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature where available (for more information, see http://www.icer-review.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/).

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[6]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair*: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs. Specifically, for this review, differences in baseline characteristics and/or duration of follow-up were allowed only if appropriate statistical methods were used to control for these differences (e.g., multiple regression, survival analysis).*

Poor*: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

PICOTS Inclusion Criteria

All search algorithms for the systematic literature review will be generated utilizing PICOTS related elements: Patient, Interventions, Comparisons, Outcomes, Timing, and Setting.

Population

The population of focus for the review will be adults with multiple myeloma whose disease has not responded to at least one previous line of treatment (i.e., refractory) or has relapsed following such treatment, are not currently on maintenance treatment, and are not being considered for stem cell transplant.

Interventions

The interventions of interest are listed below. Regimens listed are based on FDA-labeled indications for treatment of relapsed/refractory disease as well as expert input regarding common treatment approaches for the populations of interest.

- Carfilzomib with lenalidomide and dexamethasone
- Daratumumab monotherapy
- Elotuzumab with lenalidomide and dexamethasone
- Ixazomib with lenalidomide and dexamethasone
- Panobinostat with bortezomib and dexamethasone
- Pomalidomide with low-dose dexamethasone

Comparators

The primary comparators of interest will be the historical standard treatments for this population, either lenalidomide or bortezomib in combination with dexamethasone. We recognize, however, that several recent trials have involved comparisons to dexamethasone alone and/or placebo, or have been studied using single-arm designs alone. To account for these differences, results will be presented on an overall basis as well as stratified by type of comparator where necessary.

Outcomes

This review will examine key clinical outcomes associated with multiple myeloma, including surrogate outcomes common to cancer trials. In order to inform considerations regarding possible treatment sequencing, results will be summarized on an overall basis as well as stratified by number of prior treatments where such data are available. Outcomes of interest will include:

- Overall survival
- Disease progression-related measures (progression-free survival, time to progression)
- Biochemical response (overall response rate)
- Duration of response
- Symptom control
- Health-related quality of life
- Treatment-related adverse events:
    - Rates of key adverse events by type (e.g., systemic, nervous system, blood/lymphatic, etc.)
    - Rates of Grade 3 or 4 key adverse events
    - Discontinuation due to adverse events

Evidence tables will be developed for each selected study, and results will be summarized in qualitative fashion. In addition, quantitative indirect comparisons of certain outcomes using Bayesian network meta-analysis will be considered where feasible.

Timing

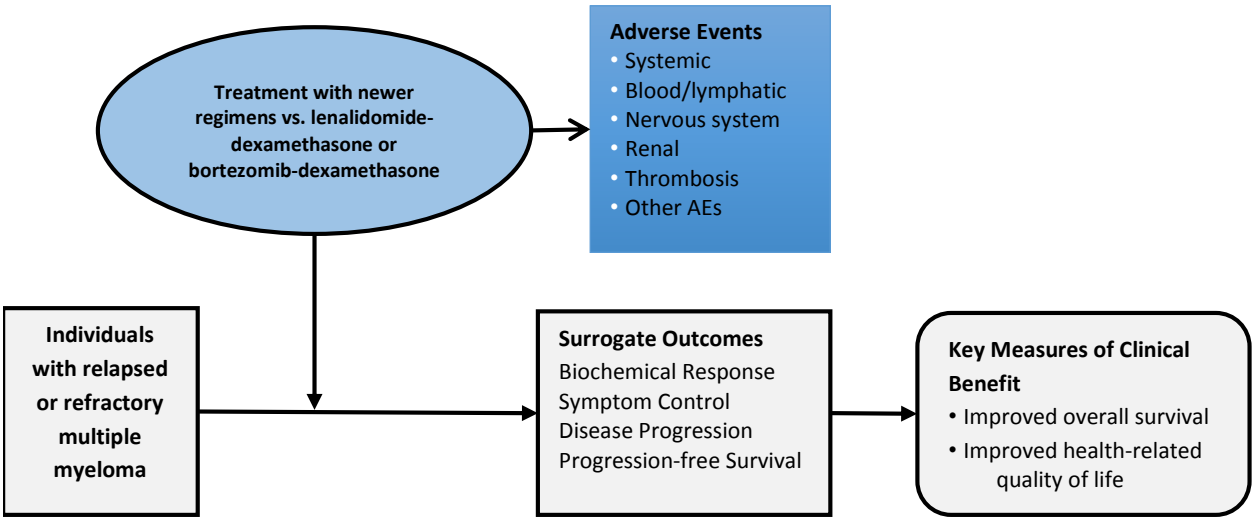
Evidence on intervention effectiveness and harms will be derived from studies of any duration and time period.

Setting

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Analytic Framework

The proposed analytic framework for this project is depicted below.



EVIDENCE REVIEW METHODS

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on multiple myeloma will follow established best methods.[7,8] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English-language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. The search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 on the following pages. We will also include abstracts from conference proceedings in the literature search. In order to supplement the above searches and ensure optimal and complete

literature retrieval, we will perform a manual check of the references of recent relevant reviews and meta-analyses.

Table 1: Search Strategy of Medline 1996 to Present with Daily Update, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 20, 2016, EBM Reviews - Cochrane Central Register of Controlled Trials December 2015

1	exp multiple myeloma/	19476
2	myelom$.ti,ab.	29327
3	plasm$ cell myelom$.ti,ab.	291
4	myelomatosis.ti,ab.	100
5	(plasm$ adj3 neoplas$).ti,ab.	855
6	kahler.ti,ab.	46
7	(pomalidomide or pomalyst or imnovid).ti,ab.	242
8	(panobinostat or farydak).ti,ab.	259
9	(ixazomib or ninlaro).ti,ab.	31
10	(elotuzumab or empliciti).ti,ab.	47
11	(daratumumab or darzalex).ti,ab.	27
12	(carfilzomib or kyprolis).ti,ab.	260
13	1 or 2 or 3 or 4 or 5 or 6	32146
14	7 or 8 or 9 or 10 or 11 or 12	759
15	13 and 14	432
16	limit 15 to english language	411
17	limit 16 to humans	404
18	(addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or interview or lectures or letter or monograph or news or practice guideline or "review" or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt.	2710272
19	17 not 18	244
Date of Search: February 9, 2016		

Table 2: Search Strategy of Embase on February 9, 2016

#19	#17 AND ('clinical study'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'controlled study'/de OR 'human'/de OR 'in vivo study'/de OR'intention to treat analysis'/de OR 'multicenter study'/de OR 'normal human'/de OR 'open study'/de OR 'phase 1 clinical trial'/de OR 'phase 1 clinical trial (topic)'/de OR 'phase 2 clinical trial'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial'/de OR 'phase 3 clinical trial (topic)'/de OR 'randomized controlled trial (topic)'/de) AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it)	1,004
#18	#17 AND ('clinical study'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'controlled study'/de OR 'human'/de OR 'in vivo study'/de OR'intention to treat analysis'/de OR 'multicenter study'/de OR 'normal human'/de OR 'open study'/de OR 'phase 1 clinical trial'/de OR 'phase 1 clinical trial (topic)'/de OR 'phase 2 clinical trial'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial'/de OR 'phase 3 clinical trial (topic)'/de OR 'randomized controlled trial (topic)'/de)	1,059
#17	#16 NOT [medline]/lim	1,059
#16	#15 NOT #1	1,282
#15	#12 AND #13 AND #14	1,296
#14	[humans]/lim	16,611,641
#13	[english]/lim	24,861,059
#12	#9 AND #11	1,426
#11	#2 AND #10	44,897
#10	'myeloma':ti OR 'myeloma':ab	62,729
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	2,457
#8	'pomalidomide':ti OR 'pomolidomide':ab OR 'pomalyst':ti OR 'pomalyst':ab	408
#7	'panobinostat':ti OR 'panobinostat':ab OR 'farydak':ti OR 'farydak':ab	800
#6	'daratumumab':ti OR 'daratumumab':ab OR 'darzalex':ti OR 'darzalex':ab	161
#5	'ixazomib':ti OR 'ixazomib':ab OR 'ninlaro':ti OR 'ninlaro':ab	126
#4	'elotuzumab':ti OR 'elotuzumab':ab OR 'empliciti':ti OR 'emplicity':ab	147
#3	'carfilzomib':ti OR 'carfilzomib':ab OR 'kyprolis':ti OR 'kyprolis':ab	1,040
#2	'multiple myeloma'/exp	61,760
#1	'case report'/it OR 'case study'/it OR 'letter'/it OR 'editorial'/it	1,401,557

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will screen the titles and abstracts of all publications identified through electronic searches according to the inclusion and exclusion criteria defined by the PICOTS elements; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

For the systematic literature review, the data extraction will be performed in the following steps:

1. Two reviewers will extract information from the full articles.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Information from the accepted studies will be extracted into data extraction forms.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, multiple assessments of publication bias will be performed. We will first scan the ClinicalTrials.gov site to identify studies completed more than 2 years ago which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies, in order to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables, and synthesized qualitatively in the text of the report. An evidence table shell is presented in Appendix B.

In addition, quantitative indirect comparisons using Bayesian network meta-analysis (NMA) will be considered where possible.[11] Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points will be used to assess model fit under multiple alternative assumptions. Given the large number of comparisons to be made among multiple myeloma treatments, and the expectation of at least some degree of heterogeneity in patient populations and/or study design, there is a general preference for a random-effects approach. However, the network is also expected to be constructed of primarily single-study connections, which may limit the feasible approach to use of a fixed-effects model (to preserve statistically-significant effects observed in trials) and selected subgroup analyses (to address heterogeneity).[12]

Quantitative analyses will focus attention on the effects of the regimens of interest on progression-free and/or overall survival, and will be conducted using the NetMetaXL tool (http://www.netmetaxl.com/), a publicly-available and validated Excel-based tool for specifying and analyzing Bayesian indirect

comparisons in a WinBUGS environment. For these outcomes, adjusted hazard ratios from the randomized trials will be log-transformed and entered into the spreadsheet, and 95% confidence intervals will be used to specify variance estimates (i.e., standard errors). A total of 40,000 iterations each will be used for both “burn-in” (for model convergence) and model (for model results) simulations.

References

1. Multiple Myeloma Research Foundation. What is multiple myeloma? http://www.themmrf.org/multiple-myeloma/what-is-multiple-myeloma/. Accessed January, 2016.

2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER Stat Fact Sheets: Myeloma. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed January, 2016.

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4. Cook R. An economic perspective on treatment options in multiple myeloma. *Managed Care Oncol.* 2007;3:10-12.

5. Jones JA, Qazilbash MH, Shih YC, Cantor SB, Cooksley CD, Elting LS. In-hospital complications of autologous hematopoietic stem cell transplantation for lymphoid malignancies: clinical and economic outcomes from the Nationwide Inpatient Sample. *Cancer.* 2008;112(5):1096-1105.

6. Appendix VII- Criteria for Internal Validity: Assessing Individual Studies. *Procedure Manual*: U.S. Preventive Services Task Force; 2011.

7. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.

8. Higgins JPT, Green S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions.* The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine.* 2009;6(7):e1000097.

10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

11. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* Oct 15 2005;331(7521):897-900.

12. Cameron C, Coyle D, Richter T, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ Open.* 2014 Jun 2;4(6):e004301. doi: 10.1136/bmjopen-2013-004301 (Supplemental Appendix 9).

APPENDIX A. PRISMA CHECKLIST

The checklist below is drawn from Moher et al. 2009.[9] Additional explanation of each item can be found in Liberati et al. 2009.[10]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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APPENDIX B. DATA EXTRACTION SUMMARY TABLE SHELL

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms