Indirect costs of oral versus non-oral therapies in hematologic malignancies: A systematic literature review

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Disclosures

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Background and objective

Background

- Hematological cancers are generally categorized as leukemia, lymphoma, or myeloma, depending on the primary site affected[1]
- In 2020, there were an estimated 178,520 new hematological cancer cases in the USA[2]
  - AML was the most common form of leukemia, with an estimated 19,940 new cases
- The treatment landscape for hematologic malignancies is evolving rapidly, and a range of therapeutic options with differing routes of administration is now available
- The shifting dynamics of these novel therapies and increasing total treatment costs highlight the importance of value-based healthcare decisions that take patient, payer, and societal perspectives into account
- It is therefore increasingly important to consider both direct and indirect costs when evaluating therapeutic options
- Moreover, reducing healthcare visits for administration of non-oral (injectable or mixed) therapies results in indirect cost savings and is of particular relevance during the COVID-19 pandemic, given the distinct challenges with visiting hospital settings

Objective

- To assess the differences in indirect non–treatment-related costs between oral and non-oral therapies for hematologic malignancies

AML, acute myeloid lymphoma.

1. Gonzalez-McQuire S, et al. *J Med Econ* 2018;21:450–467; 2. Siegel RL, et al. *CA Cancer J Clin* 2020;70:7–30.

Methods

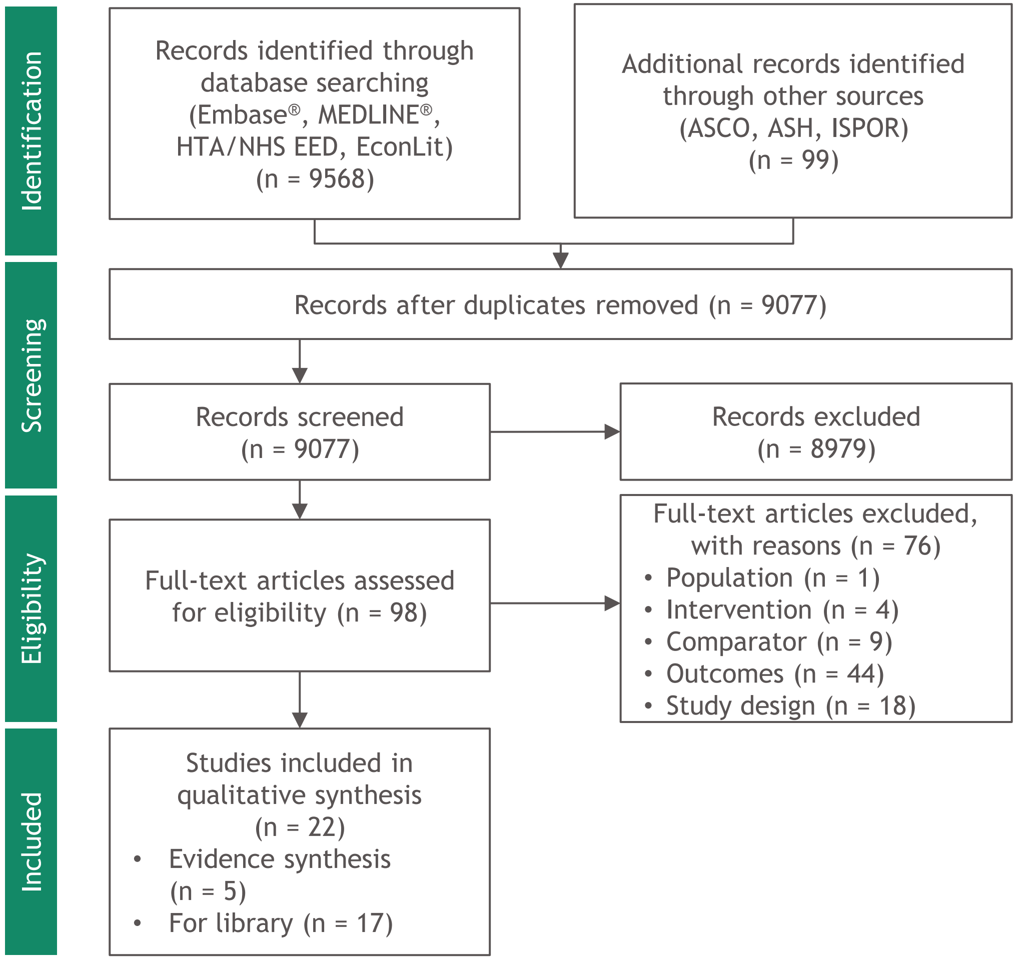
- A systematic literature review was conducted by searching Embase®, MEDLINE®, HTA/NHS EED, and EconLit databases from inception to October 2020
  - Approved medications with both oral and non-oral formulations for hematologic malignancies were identified from a targeted search of US FDA and EMA databases
- Searches of proceedings from the 2018–2020 ASCO, ASH, and ISPOR conferences, and a manual search of the reference list from all included study publications were also performed
- After exclusion of duplicates, two investigators reviewed all abstracts and proceedings identified through the searches and applied PICO criteria[1] to assess eligibility
  - Studies were included if patients with hematological cancers were receiving medications with both oral and non-oral formulations approved for treatment of hematological cancers
  - The full-text studies identified for eligibility included cost components such as those related to healthcare visits for therapy, and included out-of-pocket costs associated with travel, time burden of patients and caregivers, as well as lost productivity accruing to employers and society

ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA/NHS EED, Health Technology Assessment/National Health Service Economic Evaluation Database; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; PICO, Population, Intervention, Comparator, and Outcome.
1. Cochrane Handbook for Systematic Reviews of Interventions (v6.1): https://training.Cochrane.org/handbook/PDF/v6.1.

Included studies

- A total of 9667 records were identified
- After duplicates were removed, 9077 records were screened by title and abstract, resulting in 98 publications being selected for full-text screening
  - A total of 22 studies were included in qualitative synthesis
  - Five studies conducted in the USA (n = 3),[1-3] Italy (n = 1),[4] and Finland (n = 1)[5] were identified as eligible for evidence synthesis and summarization
  - The remaining 17 studies were used for the library of which 14 studies summarized the effects of the COVID-19 pandemic on access to care for patients with hematological cancer. As these studies were in the form of narrative reviews or clinical guideline recommendations, they were not included in evidence synthesis

PRISMA diagram



1. Chari AR, et al. *Oncologist* 2019;24:1479–1487; 2. Ailawadhi SD, et al. *Clin Ther* 2019;41:477–93.e477; 3. Merola DY, et al. *J Manag Care Spec Pharm* 2018;24:1019–1026; 4. Ripellino CP, et al. *Value Health* 2018;21(suppl 3):S48; 5. Salonen JT, et al. *Clin Lymphoma Myeloma Leuk* 2019;19(suppl):e224–e225.

Study characteristics

Publication	Country	Indication	Sample size	Cost elements assessed
Chari et al. 2019[1]	USA	RRMM	160	Time and transportation burden for patient and/or caregiver, co-payment for doctor visits
Ailawadhi et al. 2019[2]	USA	RRMM	NR	Productivity loss, transportation and/or caregiving services
Merola et al. 2018[3]	USA	MM	299	Productivity loss
Ripellino et al. 2018[4]	Italy	RRMM	NR	Not specified
Salonen et al. 2019[5]	Finland	MM	97	Transportation

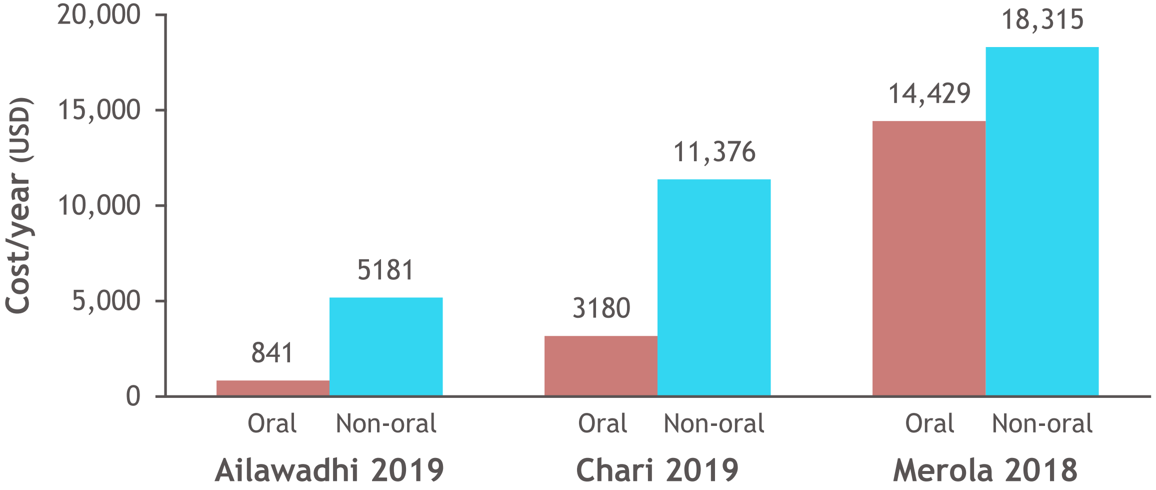
- Of the 5 studies identified for evidence synthesis:
  - Three were observational studies conducted between January 2008 and July 2017[1,3,5]
  - Two were cost-offset models conducted in 2018[4] and 2019[2]
- Patient median age was reported in 3 studies and ranged between 52 and 70 years[1,3,5]
  - On average, 55.5% (±18.2% SD) of participants were male[1,3,5]
  - Only one study (Chari 2019) reported ethnicity: 85.0% of patients were white, 10.6% were non-white, and 4.4% had missing data[1]

MM, multiple myeloma; NR, not reported; RRMM, relapsed/refractory multiple myeloma; SD, standard deviation.

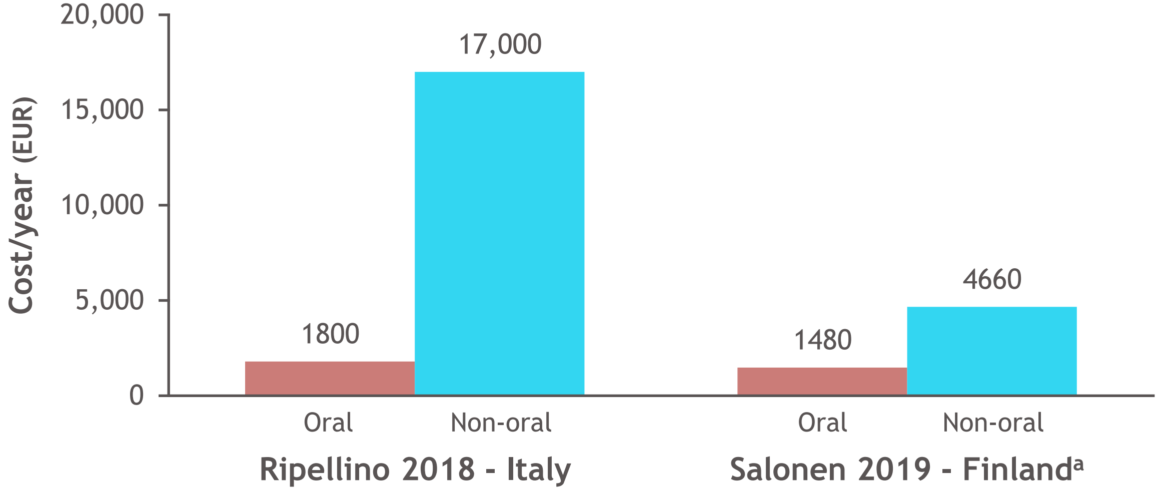
1. Chari AR, et al. *Oncologist* 2019;24:1479–1487; 2. Ailawadhi SD, et al. *Clin Ther* 2019;41:477–93.e477; 3. Merola DY, et al. *J Manag Care Spec Pharm* 2018;24:1019–1026; 4. Ripellino CP, et al. *Value Health* 2018;21(suppl 3):S48; 5. Salonen JT, et al. *Clin Lymphoma Myeloma Leuk* 2019;19(suppl):e224–e225.

Indirect treatment costs

Annual indirect cost of treatment for US-based studies



Annual indirect cost of treatment for Europe-based studies

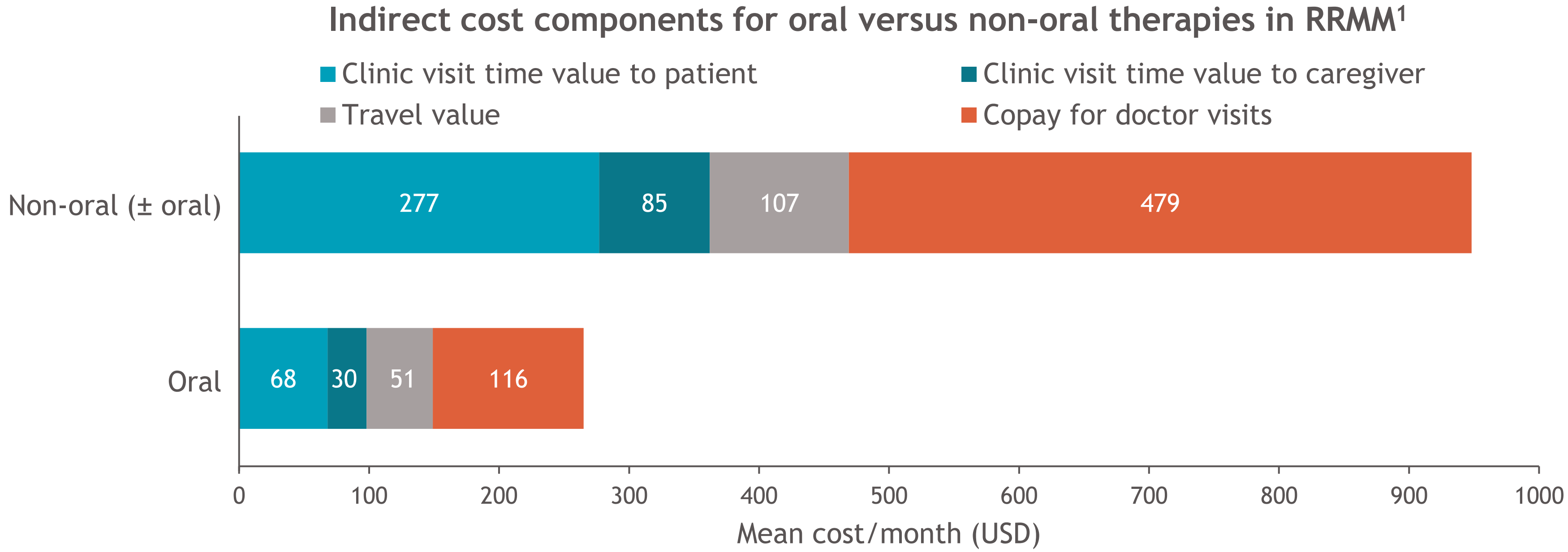


- Among all 5 studies, total indirect costs for patients with MM were lower for oral versus non-oral therapies[1-5]
- In US-based studies, indirect costs were USD 841–14,429 per year for oral therapies versus USD 5181–18,315 per year for non-oral therapies[1-3]
- In Europe-based studies, indirect costs for oral versus non-oral therapies were EUR 1800 versus EUR 17,000 per year (Italian study),[4] and EUR 1480 versus EUR 4660 per year (Finnish study)[5]
- Mean difference between oral and non-oral treatments was reported only in Merola 2018 (USD 3886; 95% CI 3540-4231; $P < 0.001$)[3]

[a]Average annual costs calculated from reported monthly range (oral: 75–152 EUR per 28 days; non-oral: 267–448 EUR per 28 days).

1. Chari AR, et al. *Oncologist* 2019;24:1479–1487; 2. Ailawadhi SD, et al. *Clin Ther* 2019;41:477–43.e477; 3. Merola DY, et al. *J Manag Care Spec Pharm* 2018;24:1019–1026; 4. Ripellino CP, et al. *Value Health* 2018;21(suppl 3):S48; 5. Salonen JT, et al. *Clin Lymphoma Myeloma Leuk* 2019;19(suppl):e224–e225.

Indirect cost components



- Chari et al. 2019 reported indirect cost components for oral versus non-oral therapies[1]
  - Monthly mean costs were significantly lower in the oral versus non-oral groups for patient time value (P < 0.001), caregiver time value (P < 0.01), and doctor visit copay (P < 0.01)
- Two studies estimated productivity loss with the first modeling costs for a US population[2] and the second using real-world data from large US health and insurance databases[3]
  - Both studies found oral therapies to be associated with less burden on patient productivity compared with non-oral therapies

1. Chari AR, et al. *Oncologist* 2019;24:1479–1487; 2. Ailawadhi SD, et al. *Clin Ther* 2019;41:477–93.e477; 3. Merola DY, et al. *J Manag Care Spec Pharm* 2018;24:1019–1026.

Implications of COVID-19 pandemic

Treatment recommendations on the use of oral and injectable therapies during the COVID-19 pandemic in (A) AML and (B) MM patient populations

(A)

Patients with AML during COVID-19 outbreak

- General recommendation: switch patients from an IV or SC treatment to a fully oral treatment combination as much as possible
- Elderly/frail patients: outpatient treatment with an oral targeted agent is preferred, where feasible

Induction
- General recommendation: consider outpatient induction when feasible
- Elderly/frail patients: Patients undergoing chemotherapy, especially those > 50 years, should be treated in an inpatient setting

Consolidation
- Administer consolidation therapy in an outpatient setting (utilizing IV pumps)

Maintenance
- No recommendations on the use of oral vs injectable therapies

Relapsed/refractory
- Outpatient treatment with an oral targeted agent is preferred, where feasible

(B)

Patients with MM during COVID-19 outbreak

- General recommendation: switch patients from an IV or SC treatment to a fully oral treatment combination as much as possible

Newly diagnosed
- General recommendation: if possible, oral regimens are preferred over injectable therapies
- Elderly/frail and transplant ineligible patients: treatment with regimens including only oral drugs should be pursued

Low priority
- Postpone follow-up visits
- No recommendations on the use of oral vs injectable therapies

Intermediate priority
- Young/fit and transplant eligible patients: consider delaying ASCT via additional induction cycles and/or lenalidomide maintenance
- Elderly/frail and transplant ineligible patients: prefer prescription of orally available drugs; in patients responding to lenalidomide-dexamethasone, consider discontinuation of dexamethasone and maintain response with lenalidomide alone

High priority
- Continue therapy on a case-by-case basis
- No recommendations on the use of oral vs injectable therapies

Relapsed/Refractory
- Consider prescribing orally administered agents over IV or SC treatments on a case-by-case basis[a]

Maintenance and/or remission
- Give preference to regimens that allow for limited exposure to health care facilities
- Allow for substitution of IV chemotherapy with oral regimens and/or minimize dosing frequency

- Across the 14 studies reporting implications of COVID-19 on treatment access and indirect costs, all generally advised against inpatient treatment regimens to reduce the risk of SARS-CoV-2 infection[1-14]
  - Recommendations for treatment alterations due to COVID-19 were tailored to patients with MM, AML, and CLL, in addition to mixed hematological cancer populations
  - For cases in which minimal impact on treatment effectiveness is expected, oral therapies were recommended to mitigate the risk of COVID-19 infection and relieve strain on the healthcare system by decreasing the need for in-hospital visits[1,2,4,6,12,14]
- Publications often stratified patient populations according to risk status, recommending oral therapies for: newly diagnosed and/or standard risk MM, medium priority elderly transplant non-eligible MM patients, relapsed/refractory MM, CLL, unfit or refractory AML, frail/elderly AML patients, low priority NHL, high priority indolent NHL, and HL[1-14]

[a]Hungria 2020 recommended continuing infusion treatments.[4]

ASCT, autologous stem cell transplantation; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; IV, intravenous; NHL, non-Hodgkin lymphoma; SC, subcutaneous.

1. Al Saleh AS, et al. *Acta Haematol* 2020;143:410–416; 2. Aleem A, et al. *J Appl Hematol* 2020;11:41–50; 3. Garg PK, et al. *J Surg Oncol* 2020;122:579–593; 4. Hungria V, et al. *Hematol Transfus Cell Ther* 2020;42:200–205; 5. Isidori A, et al. *Front Oncol* 2020;10:1439; 6. Jain A, et al. *Indian J Hematol Blood Transfus* 2020;36:605–615; 7. Kurniawan A, et al. *Asian J Oncol* 2020;DOI:10.1055/s-0040-1716813; 8. Malard F, Mohty M. *Lancet Haematol* 2020;7:e435–e437; 9. Paul S, et al. *Acta Haematol* 2020;DOI:10.1159/000508199; 10. Percival M-EM, et al. *JCO Oncol Pract* 2020;16:571–578; 11. Raza A, et al. *Leuk Res Rep* 2020;DOI:10.1016/j.lrr.220.100201; 12. Sehn LH, et al. *Curr Oncol* 2020;27:e332–e335; 13. Terpos, E et al. *Leukemia* 2000;34:2000–2011; 14. Wilde L, et al. *Front Oncol* 2020;10:1689.

Summary

- To our knowledge, this is the first systematic literature review to assess indirect costs associated with oral versus non-oral therapies in hematologic malignancies
  - A key finding was the scarcity of research addressing indirect costs
- Despite the low number of eligible studies, all included studies supported the same conclusion: oral therapies are associated with lower indirect costs compared with non-oral therapies in multiple myeloma
- Reduction in healthcare visits is a major cost benefit of oral therapy, with clear cost savings for the healthcare system as well as patients and society
  - Furthermore, reducing healthcare visits is recommended during the current pandemic with recent literature proposing oral treatments to mitigate the risk of SARS-CoV-2 infection
- From a societal perspective, the lower indirect costs associated with oral therapies make them preferable in the treatment of hematological cancers compared with their non-oral counterparts
- Preference for an oral therapy can be a factor for improving adherence to treatment
  - One study showed that oral therapy for relapsed/refractory MM was predictive of treatment satisfaction (perceived treatment convenience)[1]
- While the evidence base for indirect costs associated with oral versus non-oral therapies in hematologic malignancies is still in its early stages, the value of oral regimens is already evident when considering a broader economic perspective

1. Chari AR, et al. *Oncologist* 2019;24:1479–1487.

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- For questions please visit: www.globalbmsmedinfo.com