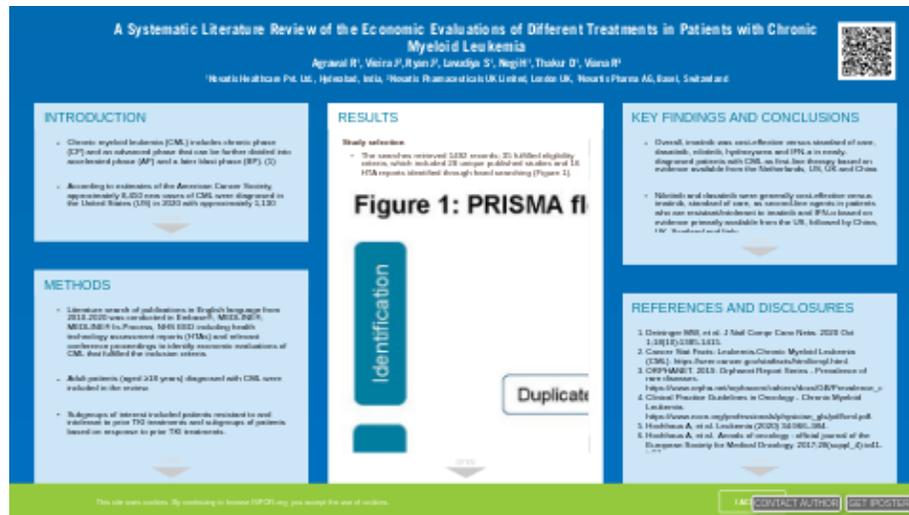


A Systematic Literature Review of the Economic Evaluations of Different Treatments in Patients with Chronic Myeloid Leukemia



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INTRODUCTION

- Chronic myeloid leukemia (CML) includes chronic phase (CP) and an advanced phase that can be further divided into accelerated phase (AP) and a later blast phase (BP). (1)
- According to estimates of the American Cancer Society, approximately 8,450 new cases of CML were diagnosed in the United States (US) in 2020 with approximately 1,130 deaths due to CML. (2) An estimated prevalence of 0.125 per 10,000 individuals of all ages was reported for Europe in 2016. (3)
- The current standard of care for patients with CP-CML are the tyrosine kinase inhibitors (TKIs), the 5-year survival rates are around 70% including patients receiving TKI treatment in 3L. (4-7)
- Management of CML is associated with extensive economic burden. The objective of systematic literature review (SLR) was to conduct a comprehensive assessment of economic evaluations in CML.

METHODS

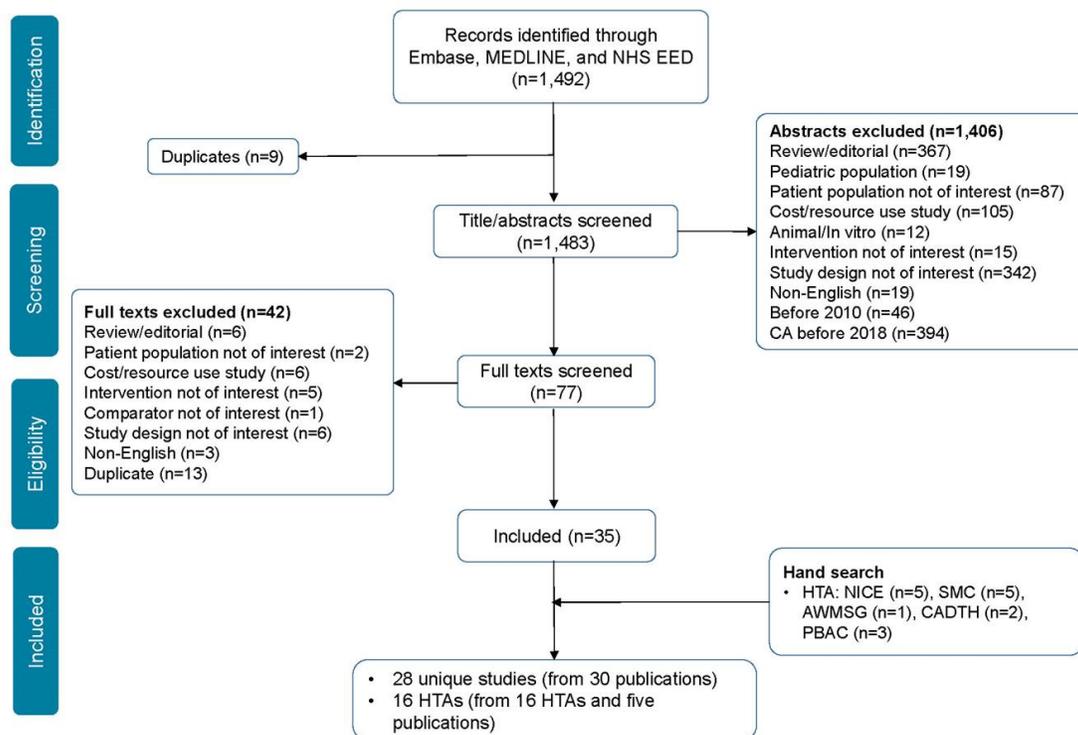
- Literature search of publications in English language from 2010-2020 was conducted in Embase®, MEDLINE®, MEDLINE® In-Process, NHS EED including health technology assessment reports (HTAs) and relevant conference proceedings to identify economic evaluations of CML that fulfilled the inclusion criteria.
- Adult patients (aged ≥ 18 years) diagnosed with CML were included in the review.
- Subgroups of interest included patients resistant to and intolerant to prior TKI treatments and subgroups of patients based on response to prior TKI treatments.
- Patients with CML in advanced phases were excluded.
- The interventions of interest were asciminib, nilotinib, imatinib, dasatinib, bosutinib, ponatinib, interferon (broad spectrum), allogeneic stem cell transplantation (Allo-SCT), homoharringtonine (omacetaxine) and best supportive care (including hydroxycarbamide).
- Screening and extractions were performed through two reviewer process. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer.
- Data from the included studies were extracted by one reviewer and the quality and completeness of the data were thoroughly checked by the second reviewer.
- All the extracted studies were critically appraised using the Drummond's checklist. (8)

RESULTS

Study selection

- The searches retrieved 1492 records; 35 fulfilled eligibility criteria, which included 28 unique published studies and 16 HTA reports identified through hand searching (Figure 1).

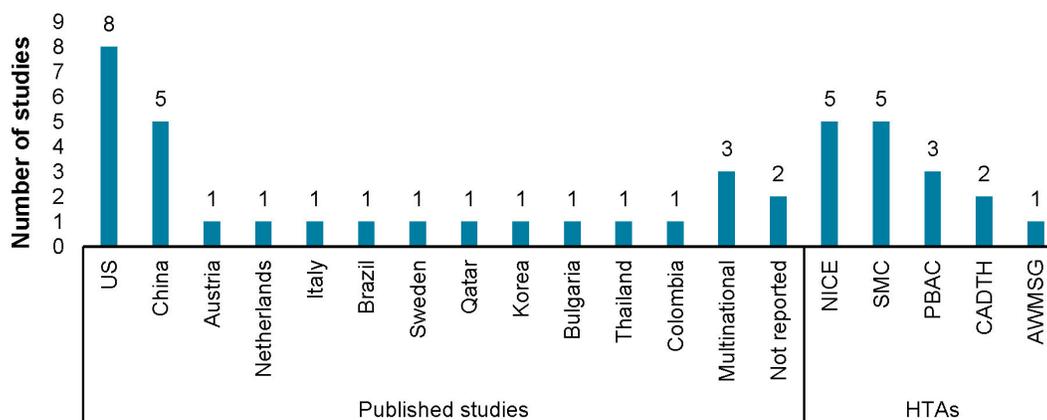
Figure 1: PRISMA flow diagram for the SLR



AWMSG: All Wales Medicines Strategy Group, CA: Conference abstract, CADTH: Canadian Agency for Drugs and Technologies in Health, HTA: Health technology assessment, NHS EED: National Health Services Economic Evaluation Database, NICE: National Institute for Health and Care Excellence, PBAC: Pharmaceutical Benefits Advisory Committee, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SLR: Systematic literature review, SMC: Scottish Medicines Consortium

Study characteristics

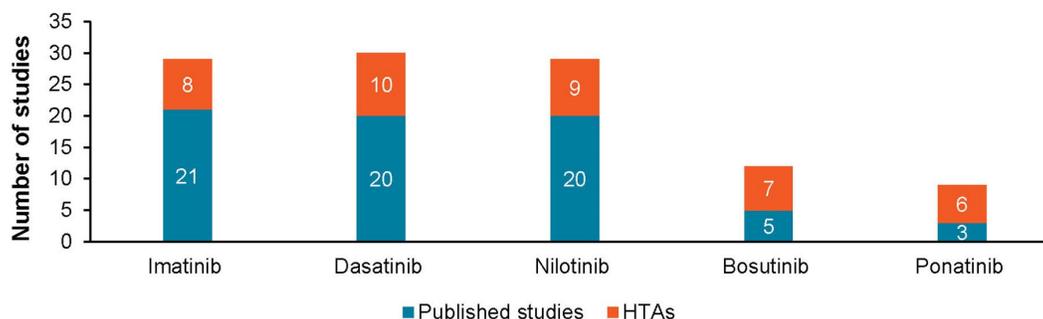
- Fifteen studies and six HTAs included patients with CP-CML, whereas 13 studies and five HTAs did not mention stage of CML. Five HTAs included patients with CP-, AP- or BP-CML.
- Majority of studies evaluated first-line treatment with TKIs.
- Included studies were conducted across 14 countries, with most studies conducted in the US (n=8), followed by China (n=5) (Figure 2).

Figure 2: Overview of the published studies by country of publication

AWMSG: All Wales Medicines Strategy Group, CADTH: Canadian Agency for Drugs and Technologies in Health, HTA: Health technology assessment, NICE: National Institute for Health and Care Excellence, PBAC: Pharmaceutical Benefits Advisory Committee, SMC: Scottish Medicines Consortium, US: United States

Interventions and type of economic evaluation

- Treatments evaluated included imatinib, dasatinib, nilotinib, ponatinib and bosutinib (Figure 3).

Figure 3: Interventions assessed for the economic evaluation

HTA: Health technology assessment

NOTE: Each study evaluated more than one treatment; therefore, the total number of studies exceed 28. Similar was the case with HTA reports

- Majority of the journal articles and HTAs were either cost-utility or cost-effectiveness analyses.
- Payer perspective was widely used across the analyses (n=30). Four studies were conducted from a societal perspective.
- Most studies used a Markov model and the time horizon varied from ≤ 5 years to life-time.
- Twenty one published studies and fourteen HTAs performed a cost-utility analysis.
 - Most studies and HTAs reported cycle length of 1 month (Range: 1-12 months).

Economic evaluation of TKIs in the treatment of CML

First-line treatment

- Fifteen studies and six HTAs conducted economic evaluations of first-line TKIs (Figure 4a).
- As first-line therapy, imatinib was cost-effective in six studies as compared to standard-of-care, nilotinib and dasatinib in 2 studies each. (9-13)
- Nilotinib was found cost-effective versus imatinib and dasatinib in five studies. (14-17)

- Evidence was available from the Netherlands, US, UK and China

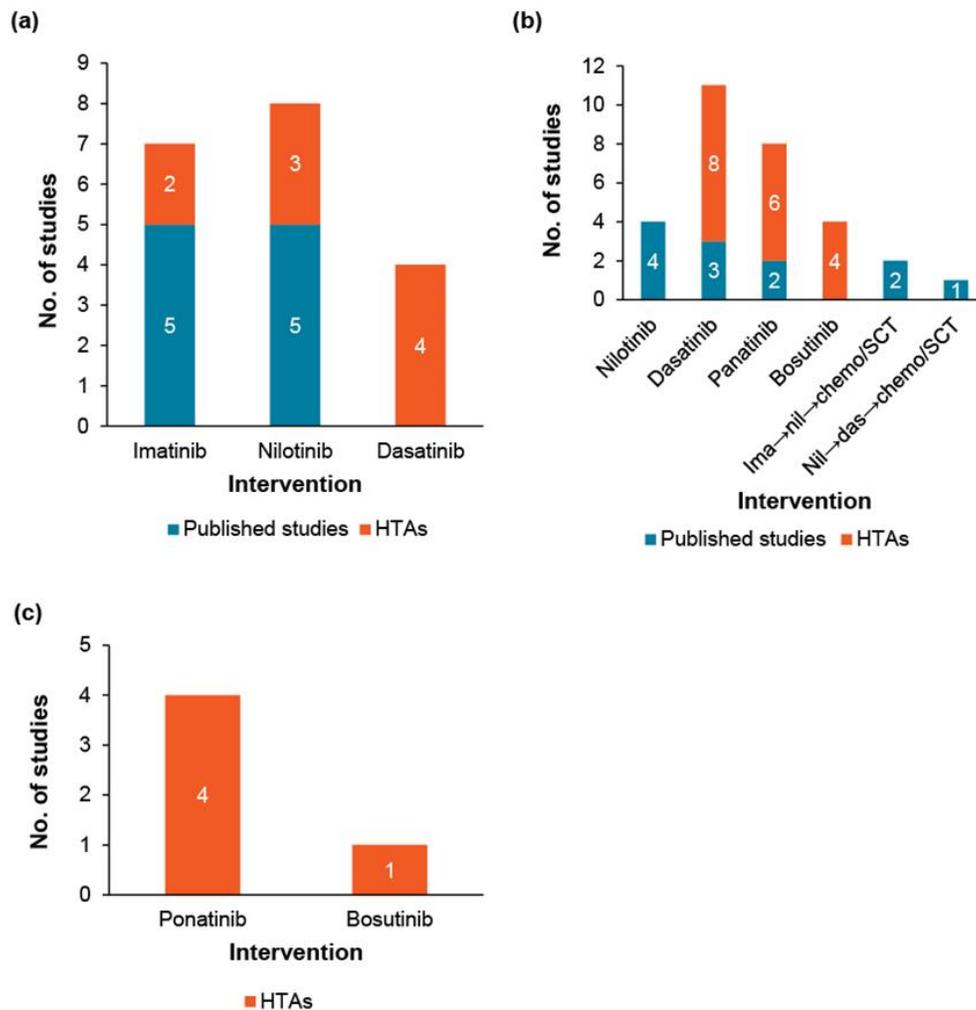
Second-line treatment

- Nine studies and seven HTAs conducted economic evaluations of second line TKIs (Figure 4b).
- As second-line therapy, nilotinib and dasatinib were found to be cost-effective versus high-dose imatinib. (18)
- Under patient access schemes bosutinib and dasatinib were cost-effective as compared with hydroxycarbamide and imatinib/nilotinib, respectively. (19, 20)
- Evidence was primarily available from the US, followed by China, UK, Scotland and Italy

Third-line treatment

- One study and two HTAs from NICE conducted economic evaluations of third line TKIs (Figure 4c).
- Ponatinib was cost-effective versus interferon alpha (INF- α), hydroxycarbamide, bosutinib, and Allo-SCT.21 Bosutinib was found to be cost-effective as compare to hydroxycarbamide. (20)
- For CP-CML patients, ponatinib ICERs were below £30,000 per QALY. (21)

Figure 4: Cost-effectiveness outcomes reported in published studies with first-line TKIs (a); with second-line TKIs (b); with third-line TKIs (c)



Ima→nil→chemo/SCT: Imatinib to nilotinib to chemotherapy/stem cell transplantation, Nil→dos→chemo/SCT: Nilotinib to dasatinib to chemotherapy/stem cell transplantation

Table 1: Studies/HTAs reporting cost- effectiveness (ICER/QALY) of treatment versus comparator with first-line, second-line and third-line TKIs

Study	Study country	Intervention	Comparator	Cost year	Incremental costs	ICER/LY	ICER/QALY
First-line TKIs							
Wolters et al, 2019	Netherlands	Imatinib	Standard of care (Interferon)	NR	€363,917,356	NR	€3,505
Sheng et al, 2017	China	Insurance coverage for imatinib	No insurance coverage for imatinib	2015	¥277,030	NR	¥50,641
Padula et al, 2016	US	Imatinib	Standard of care*	2013	NR	NR	\$883,730
Nguyen et al, 2019	US	Imatinib	Dasatinib	NR	NR	NR	\$883,730
		Imatinib	Nilotinib		NR	NR	NR
Adel et al, 2019	Qatar	Nilotinib	Dasatinib	NR	NR	NR	QAR 56,506
Borissov et al, 2018	Bulgaria	Nilotinib	Imatinib	NR	NR	NR	\$4,377
Zhu et al, 2018	China	Nilotinib	Imatinib	NR	NR	NR	Nilotinib dominant
Romero et al, 2014	Colombia	Nilotinib	Imatinib	NR	\$85,084.91	\$33,120.36/ PF-LYG	NR
		Nilotinib	Dasatinib		\$-44,674.02	Dominant	NR
NICE Dasatinib, nilotinib and imatinib (2016)	UK	Nilotinib	Imatinib	NR	NR	£4,701	£5,908
		Dasatinib	Imatinib		NR	£32,785	£26,305
SMC Dasatinib (2016)	Scotland	Dasatinib	Imatinib	NR	NR	NR	NR
PBAC Dasatinib (2015)	Australia	Dasatinib	Nilotinib	NR	NR	NR	NR
		Dasatinib	Imatinib		NR	NR	\$15,000 - \$45,000
SMC Nilotinib (2011)	Scotland	Nilotinib	Imatinib	NR	NR	NR	NR
PBAC Nilotinib (2011)	Australia	Nilotinib	Imatinib	NR	NR	NR	NR
NICE Imatinib (2003)	UK	Imatinib	Hydroxyurea	NR	NR	NR	£86,934
		Imatinib	IFN-α		NR	NR	£26,180
		IFN-α	Hydroxyurea		NR	NR	£2,505,364
Second-line TKIs							
Whalen et al, 2016	US	Dasatinib sequence	High-dose imatinib sequence	2014	NR	NR	\$100,000
		Nilotinib sequence	High-dose imatinib sequence		NR	NR	\$90,000
Rochau et al, 2015	Austria	Imatinib to nilotinib to chemotherapy/SCT	Nilotinib to chemotherapy/SCT	2012	€29,819	Dominated	€131,100
Rochau et al, 2015	US	Imatinib to nilotinib to chemotherapy/SCT	Imatinib to chemotherapy/SCT	2014	NR	\$260,800	\$253,500
		Nilotinib to dasatinib to chemotherapy/SCT	Imatinib to nilotinib to chemotherapy/SCT		NR	\$299,800	\$445,100
Maheshwari et al, 2019	Italy	Nilotinib	Dasatinib	NR	€-44,600	NR	NR
Li N et al, 2017	US	Nilotinib	Dasatinib	2015	\$-12,655	NR	Nilotinib had higher LY & QALY and lower cost vs dasatinib
CADTH Bosutinib (2015)	Canada	Bosutinib	Hydroxyurea	NR	NR	NR	CA\$ 54,290
		Bosutinib	Interferon		NR	NR	CA\$ 45,955
		Bosutinib	SCT		NR	NR	Dominant
SMC Bosutinib (2015)	Scotland	Bosutinib	Hydroxycarbamide	NR	£148,130	3.79	£39,119
SMC Dasatinib (2016)	Scotland	Dasatinib	Imatinib	NR	NR	NR	NR
NICE Dasatinib, nilotinib, and high-dose imatinib (2016)	UK	Dasatinib	Nilotinib	2009-2010	£179,087	NR	£36,251
		Dasatinib	Imatinib 400 mg		£140,707	NR	£34,907
		Dasatinib	Imatinib 600 mg		£-35,952	NR	Dominant
		Dasatinib	Imatinib 800 mg		£185,121	NR	£38,877
		Dasatinib	IFN-α		£-4,565	NR	Dominant
		Dasatinib	Nilotinib		£-9,821	NR	Dominant
AWMSG Ponatinib (2014)	Wales	Ponatinib	SCT	NR	£71,938	NR	£23,000
		Ponatinib	Dasatinib		£61,972	NR	£19,310
		Ponatinib	Bosutinib		£11,565	NR	£4,549
		Ponatinib	SCT		£78,126	NR	£14,678
		Ponatinib	Hydroxycarbamide		£-23,441	NR	Dominant
PBAC Ponatinib (2015)	Australia	Ponatinib	IFN-α	NR	NR	NR	NR
Guan et al, 2018	China	Nilotinib	Dasatinib/nilotinib	NR	NR	NR	RMB 154,330.8
Wu et al, 2017	China	Dasatinib 100 mg	Imatinib 600 mg	2015	NR	NR	\$16,417
Yue et al, 2019	US	Dasatinib	Nilotinib	NR	NR	NR	\$79,114.19
		Ponatinib	Dasatinib		NR	NR	\$176,301.60
		Ponatinib	Nilotinib		NR	NR	\$141,588
Third-line TKIs							
NICE Ponatinib (2017)	UK	Ponatinib	Bosutinib	2014-2015	NR	£15,006	£18,213
		Ponatinib	IFN-α		NR	£5,263	£6,395
		Ponatinib	Hydroxycarbamide		NR	£12,492	£15,200
		Ponatinib	Allo-SCT		NR	£4,042	£3,883
NICE Bosutinib (2016)	UK	Bosutinib	Hydroxycarbamide	NR	NR	NR	NR

Allo-SCT: Allogeneic stem cell transplantation, AWMSG: All Wales Medicines Strategy Group, CA\$: Canadian dollar, CADTH: Canadian Agency for Drugs and Technologies in Health, ICER: Incremental cost-effectiveness ratio, IFN-α: Interferon alpha, LY: Life-year, NICE: National Institute for Health and Care Excellence, NR: Not reported, PBAC: Pharmaceutical Benefits Advisory Committee, PF-LYG: Progression-free life-years gained, QALY: Quality-adjusted life-year, RMB: Renminbi, SCT: Stem cell transplantation, SMC: Scottish Medicines Consortium
*Physician's choice (any of the three approved TKIs; Imatinib, Dasatinib or Nilotinib)

KEY FINDINGS AND CONCLUSIONS

- Overall, imatinib was cost-effective versus standard of care, dasatinib, nilotinib, hydroxyurea and IFN- α in newly-diagnosed patients with CML as first-line therapy based on evidence available from the Netherlands, US, UK and China
- Nilotinib and dasatinib were generally cost-effective versus imatinib, standard of care, as second-line agents in patients who are resistant/intolerant to imatinib and IFN- α based on evidence primarily available from the US, followed by China, UK, Scotland and Italy
- Limited evidence (two studies evaluating ponatinib and bosutinib) from the UK exists regarding the economic evaluations in the third-line setting.

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Conflict of Interest

Rumjhum Agrawal, Joao Vieira, Jacqueline Ryan, Sreenu Lavudiya, Harish Negi and Ricardo Viana are employees of Novartis. Deepika Thakur is former employee of Novartis.