

Costs related to adverse events in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors in Canada

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ABSTRACT

Background: Treatment options for the relatively small group of patients resistant or intolerant to imatinib, a recommended first-line therapy for chronic myeloid leukemia (CML), include nilotinib or dasatinib. Current data indicates that nilotinib and dasatinib have different side effect profiles.

Objectives: To investigate costs of adverse events (AEs) in patients receiving recommended doses of nilotinib or dasatinib for treatment of chronic and accelerated CML.

Methods: Incidence rates of grade 3/4 AEs in CML patients treated with nilotinib or dasatinib were obtained from clinical trial data. Direct medical costs for non-hematological AEs and for grade 4 anemia and thrombocytopenia, and febrile neutropenia were obtained from Ontario Case Costing Initiative (OCCI) inpatient databases and were specific to oncology patients. Costs for grade 3 anemia, thrombocytopenia, and non-febrile neutropenia were assumed to be outpatient costs and were based on literature and expert validation of treatment pathway and resource utilization in the Canadian context. Multivariate sensitivity analyses were conducted on costs of AEs and for an alternative dasatinib dosing (100mg).

Results: Cost of treatment-related AEs for CML patients was highest for dasatinib. Total costs for AEs associated with the accelerated phase were higher than those associated with the chronic phase: \$19,902 versus \$7,653 for dasatinib and \$8,645 versus \$3,790 for nilotinib, respectively. Ranking observed among treatments for base case costs of AEs was maintained for both high and low cost estimates, and for 100mg dasatinib dosing, indicating that the model was robust to variation in these parameters.

Conclusions: For patients resistant or intolerant to imatinib, costs of dasatinib-related AEs were approximately twice the costs of nilotinib-related AEs in both chronic and accelerated phases, highlighting the importance of considering the cost of AEs in economic evaluation of tyrosine kinase inhibitors. Further research is needed to evaluate the impact of AEs on healthcare expenditures.

INTRODUCTION

Canadian males have a 1 in 65 probability of being diagnosed with leukemia (females 1 in 89), and a 1 in 98 probability of dying from it (females 1 in 135). Leukemia accounts for 26% of new cases (30% of deaths) due to cancer in children, and remains the most common of childhood cancers.¹

Economic burden of leukemia is high with mean hospital costs per patient (US data) estimated at Can \$51,000.²

Imatinib mesylate (Gleevec) is recommended therapy for CML treatment. Some patients treated with imatinib develop resistance or intolerance. Two treatment options are available for resistant or intolerant patients: nilotinib and dasatinib which have different side effect profiles.^{3,4}

The objective of this study was to estimate costs of adverse events (AEs) among imatinib resistant or intolerant patients receiving nilotinib or dasatinib for chronic and accelerated phases of CML.

METHODS

1 Adverse event incidence

AEs were assumed to occur during the first year of treatment and were obtained from an analysis of clinical trial data.⁵ Grade 3/4 AEs were considered since they are the most clinically significant and only AEs with expected significant resources utilization were included.

Limited data was available on breakdown of grade 3 and grade 4 hematological AEs and conservative rate estimates were made based on available information (Table 1).

Table 1 Incidence rate of adverse events associated with treatment of CML

Adverse event	Incidence rate (%)			
	Dasatinib 100mg	Dasatinib 150mg	Nilotinib ^a	Chronic phase
Hematological events				
Anemia grade 3/4	18.0	70.0	10.0	7.9
Anemia - grade 3	15.6 ^b	38.2 ^b	3.7 ^b	4.8 ^b
Anemia - grade 4	2.4 ^b	11.7 ^b	1.3 ^b	1.1 ^b
Neutropenia	47.0	63.0	32.8 ^b	28.3
Febrile Neutropenia	2.0	11.0	1.4 ^b	1.3
Thrombocytopenia grade 3/4	48.0	83.0	23.0	28.5
Thrombocytopenia - grade 3	27.4 ^b	27.6 ^b	12.9 ^b	16.2 ^b
Thrombocytopenia - grade 4	20.6 ^b	55.4 ^b	9.9 ^b	12.3 ^b
Non-hematological events				
Gastrointestinal hemorrhage	2.0	12.0	0.9	0.9
Central nervous system hemorrhage	0.0	1.0	na	0.3
Pleural effusion	3.0	3.0	2.0	0.3
Pericardial effusion	0.3 ^b	1.0	0.9 ^b	0.3
Conductive heart failure / Cardiac dysfunction	3.0	1.0	0.0	0.3
Arrhythmia	2.0	1.0	na	0.8
Phonemia	3.0	8.0	na	0.3
Infection	4.0	8.0	na	5.3

Incidence of grade 3/4 anemia is an estimate based on rates observed in imatinib-resistant patients.⁵ na = not available. ^abreakdown of grade 3/4 thrombocytopenia is an estimate based on rates observed in phase 1 trial with imatinib. ^bbreakdown of grade 3/4 thrombocytopenia is an estimate based on rates observed in phase 1 trial with imatinib. ^cbreakdown of grade 3/4 thrombocytopenia is an estimate based on rates observed in phase 1 trial with imatinib. ^dbreakdown of grade 3/4 thrombocytopenia is an estimate based on rates observed in phase 1 trial with imatinib.

2 Costing of adverse events

Costs were estimated for one year in 2006 Canadian dollars (Can\$). Non-2006 costs were inflated to 2006 using the Canadian Consumer Price Index (Table 2).

Costs of non-hematological AEs (defined using ICD-10 codes⁶) were obtained from the Ontario Case Costing Initiative (OCCI) inpatient database and were specific to oncology patients as there were not enough cases in CML patients.

Costs of hematological AEs were obtained from OCCI (inpatient data), literature and expert validation. Grade 3 and 4 hematological AEs were treated as outpatient and inpatient respectively.

Data analysis & sensitivity analyses

The incidence and cost of AEs were combined to obtain per episode cost over one year. Calculations were performed in Microsoft Excel.

Sensitivity analyses were performed by varying costs of AEs to obtain low and high estimates for total cost of AEs. A range of 30% was applied to the OCCI inpatient base case values (Table 2). For other costs, key assumptions were varied (e.g., number of transfusions, follow-up duration, treatment duration).

Another sensitivity analysis was performed on AE incidence with lower dose of dasatinib since it has been reported that incidence of AEs is reduced with 100mg dasatinib dose^{7,8} (however this is only applicable for chronic phase myeloid leukemia). Because limited data was available for dasatinib 100mg, only AEs for which data was available for all comparators were included.^{9,10}

Table 2 Per episode costs of adverse events associated with treatment of CML

Adverse event	Cost per month of event (Can\$)	Number of weeks event (range)	Base Case Total cost per episode (low-high cost) (Can\$)	Source / Comments
Hematological events				
Anemia - grade 3	1,864.89	14 weeks	6,827.10	Schedule of benefits Ontario ¹¹ , RAMO, ¹² Manitoba cost list ¹³
Anemia - grade 4	12,895	1 event	12,895	OCCI
Neutropenia	135.60	3 weeks	135.60	Outpatient treatment ¹⁴ , Schedule of benefits Ontario ¹¹
Febrile Neutropenia	37,069	1 event	37,069	(25,862-48,213)
Thrombocytopenia - grade 3	481.55	1 event	481.55	Elig ¹⁵ , schedule of benefits Ontario ¹¹
Thrombocytopenia - grade 4	5,937	1 event ¹⁶	5,937	OCCI, Elig ¹⁵ , schedule of benefits Ontario ¹¹
Non-hematological events				
Gastrointestinal hemorrhage	12,309	1 event	12,309	OCCI
Central nervous system hemorrhage	21,451	1 event	21,451	OCCI ¹⁷
Pleural effusion	25,480	1 event	25,480	(17,036-33,134)
Pericardial effusion	17,477	1 event	17,477	OCCI
Conductive heart failure / Cardiac dysfunction	22,097	1 event	22,097	OCCI
Arrhythmia	33,588	1 event	33,588	OCCI
Phonemia	24,448	1 event	24,448	(17,116-31,782)
Infection	23,219	1 event	23,219	(10,223-36,181)

OCCI: Ontario Case Costing Initiative; RAMO: Répertoire des médicaments; Elig: Eligibilité des médicaments; Schedule of benefits Ontario: Liste des médicaments remboursés; Manitoba cost list: Liste des médicaments remboursés; Outpatient treatment: Soins ambulatoires; Schedule of benefits Ontario: Liste des médicaments remboursés; Elig: Éligibilité des médicaments; Schedule of benefits Ontario: Liste des médicaments remboursés.

RESULTS

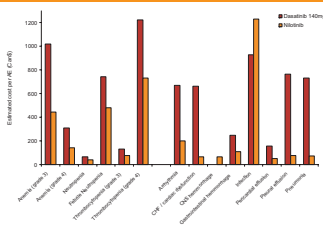
1 Costs related to chronic phase myeloid leukemia

Overall cost of treatment-related AEs was highest for dasatinib (\$7,653) compared to nilotinib (\$3,790).

Thrombocytopenia, anemia, infection and pleural effusion were biggest cost drivers for dasatinib treatment.

Infection, thrombocytopenia, febrile neutropenia and anemia were biggest cost drivers for nilotinib treatment.

Figure 1 Per patient costs of adverse events related to treatment of chronic phase myeloid leukemia



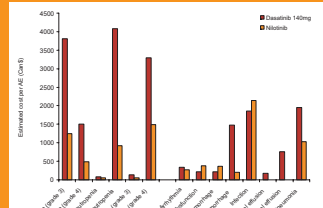
2 Costs related to accelerated phase myeloid leukemia

Total costs for AEs with accelerated phase were significantly higher than costs associated with chronic phase: \$19,902 compared with \$7,653 for dasatinib and \$8,645 compared with \$3,790 for nilotinib.

Average per patient cost of AEs was higher for dasatinib (\$19,902), than for nilotinib (\$8,645).

Febrile Neutropenia, anemia and thrombocytopenia contributed most to dasatinib AE costs, while infection, thrombocytopenia and anemia were greatest contributors to nilotinib AE costs.

Figure 2 Per patient costs of adverse events related to treatment of accelerated phase myeloid leukemia

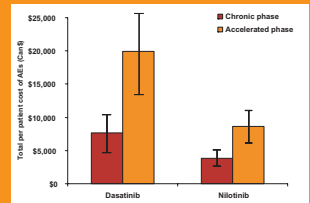


3 Sensitivity analysis

For chronic phase CML, range in overall costs of treating adverse events was larger for dasatinib than for nilotinib, and for accelerated phase CML the range in overall costs of treating adverse events was also larger with dasatinib than for nilotinib (figures 3).

- Where costs of adverse events were varied using the low and high case costs (Table 2) then the ranking observed among treatments for base case costs of AEs was maintained for both the high and low cost estimates (figure 3).

Figure 3 Costs resulting from variation of annual per patient cost of adverse events related to treatment of chronic and accelerated phase myeloid leukemia



Where incidence of adverse events was varied, using the 100mg dasatinib dose, the largest adverse event cost burden was associated with 140mg dasatinib followed by 100mg dasatinib and nilotinib (Table 3). Note this is only applicable to the chronic phase since dose reduction is not permissible with accelerated phase.

Table 3 Costs resulting from variation of incidence of AE with reduced dasatinib dose related to treatment of chronic phase myeloid leukemia

Adverse event	Annual cost per patient (Can\$)	
	Dasatinib 140mg	Dasatinib 100mg
Hematological adverse events		
Anemia (grade 3)	1,018	568
Anemia (grade 4)	309	168
Neutropenia	64	44
Febrile Neutropenia	742	519
Thrombocytopenia (grade 3)	192	76
Thrombocytopenia (grade 4)	1,223	564
Non-hematological adverse events		
CHF / cardiac dysfunction	663	0
Gastrointestinal hemorrhage	246	111
Pericardial effusion	157	157
Pleural effusion	764	510
Total	5,318	2,701

LIMITATIONS

Breakdown of grade 3/4 hematological AEs was estimated based on available data. Although actual rate values may differ, a conservative approach was taken and the same breakdown was applied for both tyrosine kinase inhibitors.

Treatment duration for anemia was based on studies with oncology patients, which usually refers to chemotherapy-induced anemia. Chemotherapy-related hematological AEs are stringent and generally stop after chemotherapy is completed. Anemia associated with a chronic treatment is likely to be more persistent and treatment duration used in this model may have underestimated actual cost of anemia.

In case of persistent treatment-related AEs, the patient may also be switched to another treatment, which is not considered in this model.

CONCLUSIONS

For patients resistant or intolerant to imatinib, costs of dasatinib-related AEs were approximately twice the costs of nilotinib-related AEs in both chronic and accelerated phases.

Ranking observed among treatments for base case total costs of AEs was maintained for both high and low cost estimates and for reduced (100mg) dasatinib dosage, indicating that the model was robust to variation in these parameters.

This study highlights the importance of considering adverse events in the economic assessment of treatment of CML patients with tyrosine kinase inhibitors.

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