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SYSTEMATIC REVIEW OF CLINICAL TRIALS AND PROSPECTIVE COHORTS: FOLLOW UP METHODS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA TREATED WITH DASATINIB

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ABSTRACT

Chronic myeloid leukemia (CML) is a malignancy of hematopoietic stem cells associated with a t(9;22) translocation that forms the Philadelphia chromosome and creates a novel fusion gene, BCR-ABL. For those who are resistant or intolerant to imatinib, second-generation tirosino-kinase inhibitor, as dasatinib, has been shown to be efficacious in all phases of the disease. Once dasatinib is taken orally and the treatment has no defined end point, a complete follow up method, including a pharmacotherapy follow up, to monitor the CML patients is essential to define adherence and treatment safety. To systematically review follow up methods of CML patients treated with dasatinib in clinical trials (CT) either randomized (RCT), or not (NRCT) and prospective cohorts (PC) a sensitized research was performed on the databases Medline (Pubmed), Cochrane Library (OVID), Embase (Elsevier) and Lilacs. Four RCT, four NRCT and three PC were identified and contained data about patients follow up, which proved to be well established and structured. Adverse drug reactions grades III and IV description was in accordance with the already published data. No pharmacotherapy follow up method has been identified, neither in CT nor in PC. The implementation of a patients follow up method is crucial to qualify the assistance and standardize the conducts. And with the presence of a pharmacist and a pharmacotherapy follow up method must be incorporated in this new role of long-term CML treatment with dasatinib in order to rationalize resources, increase the treatment efficacy and safety and improve the adherence and patient life's quality.

INTRODUCTION: Chronic myeloid leukemia (CML) is a malignancy of hematopoietic stem cells associated with a t(9;22) translocation that forms the Philadelphia chromosome and creates a novel fusion gene, BCR-ABL [1]. It is a triphasic disease, usually diagnosed in chronic phase (CP), which usually lasts 3 to 5 years [2], but ultimately progresses to accelerated phase (AP), rapidly expanding granulocytes, and blast crisis (BC), resembling acute leukemia [3].

It was estimated that in 2011, 5,150 persons (3,000 men and 2,150 women) would be diagnosed with and 270 of them will die of CML in the USA [4]. CML accounts for 15% of adult leukemias in Western countries and can occur at any age, although the incidence of the disease increases with age [5]. Hydroxyurea, busulfan, interferon alfa–based regimens, and allogeneic hematopoietic stem-cell transplant (HSCT) were the mainstays of treatment for patients with CML, until the availability of tyrosine kinase inhibitors (TKIs) [3].

The discovery of targeted tyrosine kinase inhibition of BCR-ABL kinase dramatically changed the treatment of CML.6 They are nowadays the standard of care for the treatment of CML, which is usually initiated when the diagnosis is established [1].

Treatment with molecular-targeted therapy is usually initiated with imatinib, an inhibitor of BCR-ABL tyrosine kinase approved for the US Food and Drug Administration (FDA) on May 2001. Imatinib resistance is, however, observed in some CML patients, especially in those with advanced disease [1], being considered a clinical concern, as well as imatinib intolerance. The IRIS trial, which compared imatinib with interferon plus cytarabine, indicated that approximately 30% of the 553 imatinib-treated patients with CML-CP recruited discontinued imatinib and switch to alternative agents as a result of an unsatisfactory therapeutic effect, adverse events (AEs) or other reason after median of 60 months of follow up [7].

Dasatinib is a second-generation TKI which received accelerated approval from the US FDA on June 2006 and has been shown to be efficacious in treatment of patients with CML who are resistant or intolerant to frontline chemotherapy.

Dasatinib has demonstrated to be effective for treating imatinib resistant or intolerant patients with CML in all phases of disease including CP, AP and BC [1].

Phase I dose-escalation study has shown that dasatinib has an excellent safety profile in all disease phases.8 Although the original dasatinib dosing regimen investigated in phase II studies and subsequently approved was 70 mg twice daily [9], a randomized phase III dose-optimization study led to revision of the recommended dose to 100 mg once daily in CP-CML patients, based upon non-inferior cytogenetic response rates, estimated progression free-survival and estimated overall survival, despite the lower intended total dose [10, 11]. Moreover, this regimen reduces the incidence of key toxicities (pleural effusion, neutropenia, leukocytopenia and thrombocytopenia) and is also associated with less frequent treatment-related AE overall [11].

In clinical trials of dasatinib, the AEs that arise during therapy are mostly mild to moderate in severity and are usually reversible and manageable with appropriate intervention. The most common AEs in the research populations are, besides the hematological ones (e.g. anemia, neutropenia, thrombocytopenia and leukocytopenia), gastrointestinal (e.g. diarrhea, nausea, vomiting, anorexia, abdominal pain), constitutional (e.g. pyrexia, headache, fatigue), fluid retention or bleeding events [1, 12].

Monitoring response to treatment is indispensable for effective patient care in CML [13, 14], particularly because CML has no defined treatment end point [14].

Frequent disease assessment following defined standards ensures that a patient disease is monitored appropriately and those punctual decisions can be made if and when the treatment should be changed. [13]. Furthermore, conduct long-term surveillance of recently marketed drugs is essential to quickly detect serious safety problems and not described AEs [15].

Another important and well-described issue refers to patient's adherence to TKIs, as imatinib, demonstrating to be proportional to the molecular and cytogenetic response [16]. Once dasatinib is also taken orally, a structured follow up method, including pharmaco-therapy follow up, to monitor the CML patients is essential to define the patient's adherence and the treatment safety.

There are standardized pharmacotherapy follow up methods that were developed to prevent, identify and early manage the potentials AEs by the pharmacist, in a systematic, continued and documented way, aiming to reach defined results and improve the patient life`s quality [17, 18]. For that reason, it has become an indispensable strategy to improve outcomes, reduce costs and increase adherence, especially in chronic diseases follow up [19].

Patient education by pharmacists can improve patient outcome and adherence to oral drugs used for other diseases than cancer [20]. For oral chemotherapy, pharmacy services are probably underused even in cancer centres [21]. As far as we know, there is no standardized method of pharmacotherapy follow-up of patients with CML treated with ITK.

So far, there are only few data available which focus on adherence in cancer patients treated with an oral anticancer drug [22].

Therefore, this article aims to systematically review follow up methods, including pharmacotherapy follow up, in clinical trials and prospective cohorts which included patients with CML, who were imatinib resistant/intolerant, and treated with dasatinib.

From this systematic review we intend to make a protocol of pharmacotherapy follow up to be implemented at a later.

METHODS: To systematically review and identify clinical trials either randomized (RCT), or not (NRCT) and prospective cohorts (PC), a sensitized research was performed in August 2011 on the databases Medline (Pubmed), Cochrane Library (OVID), Embase (Elsevier) and Lilacs applying the terms "Chronic myeloid leukemia" AND "Dasatinib".

Aiming to identify clinical trials, Cochrane and Clinical trials filters were applied on Medline (Pubmed) and both Cochrane Library (OVID) and Embase (Elsevier) databases, respectively, and for PC, National Institute of Health and Observational studies filters were used on Medline (Pubmed) and Embase (Elsevier), respectively. (Supplement 1) No filter was used on Lilacs since this feature was not offered in this database.

Morever, a handsearch was performed in case of database indexation failure.

The inclusion criteria were either RCT, NRCT phase II, or PC studies with CML patients, in all phases, treated with dasatinib in cases which patients had fail to achieve complete response in use of first line therapy including imatinib, or had to discontinue the treatment due to severe adverse drug reaction (ADR). This search had no language restriction.

The inquiry outcomes of this systematic review were following up methods, including pharmacotherapy follow up method, as the primary outcome, and ADR (grade III and IV), as the second.

Two investigators, L.P and P.S., independently screened the titles and abstracts of all studies identified in the literature research to verify compliance with the inclusion criteria. Data extraction and quality analysis (using Cochrane and Strobe tools for RCT and PC, respectively) was also performed independently by two investigators, with each blinded to the other's data extraction. Further information obtained from authors were requested by electronic correspondence and included in the analysis. Discrepancies in both screen and data extraction were discussed and resolution required consent from both investigators undertaking analysis and extraction.

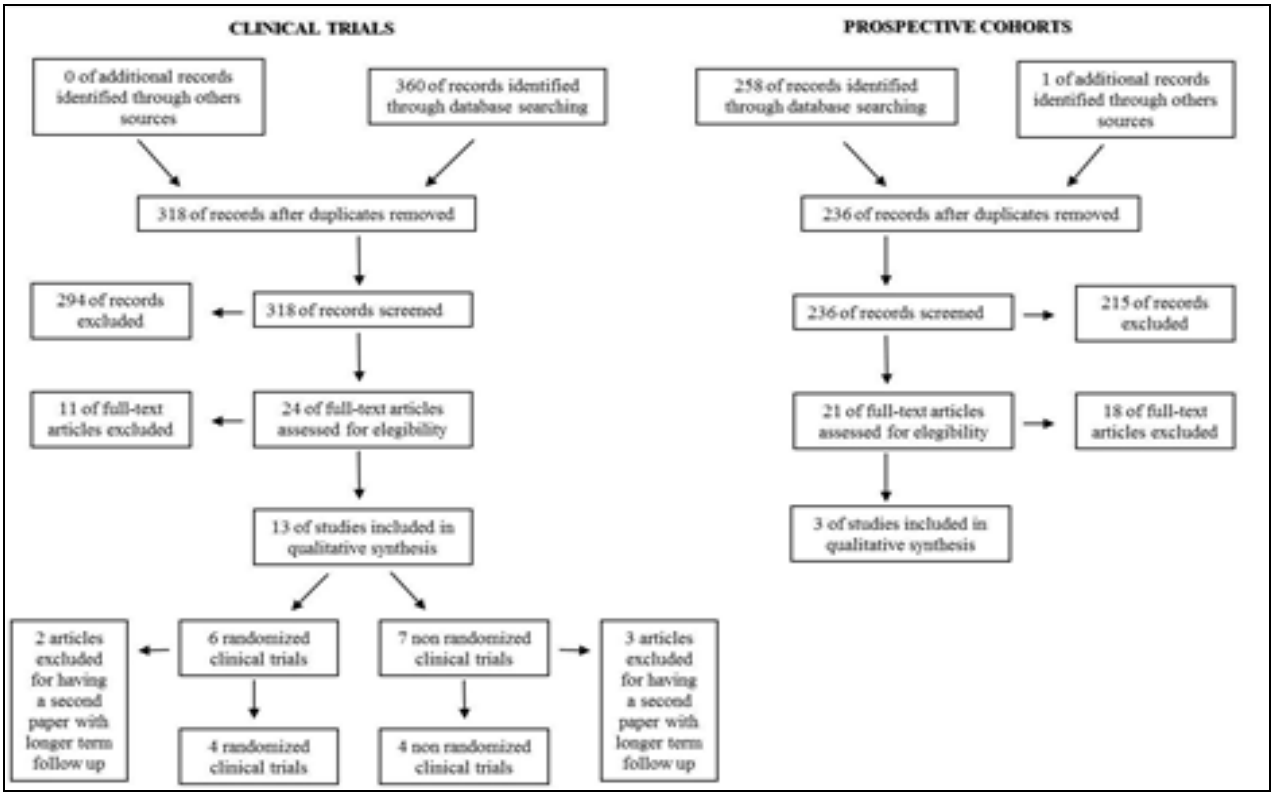
RESULTS: In the selected databases, 318 clinical trials and 235 prospective cohorts abstracts were identified (**Table 1**).

TABLE 1. SUMMARY OF CLINICAL TRIALS AND PROSPECTIVE COHORTS FOUND IN THE SELECTED DATABASES

	Clinical trials	Prospective cohorts
Medline (Pubmed)	205	48
Cochrane Library (OVID)	32	0
Embase (Elsevier)	127	204
Lilacs	6	6
Total	318*	235*

* To the total, the duplicates ones were already discounted (52 CTs and 23 cohorts).

Six RCT and seven NRCT were considered eligible for reaching all the inclusion's criteria. Five studies have a second paper with longer term of follow up published. Therefore, once the studies protocols remain the same, only the further one was included (four RCT and four NRCT). Two PCs were included. In addition, one PC study found by handsearch was also included to fulfill the entire criteria (**Flowchart 1**). Data from the included studies are described in **Table 2**, and stratified below by outcome of interest.



FLOWCHART 1: INCLUSION PROCESS OF CLINICAL TRIALS AND PROSPECTIVE COHERTS

TABLE 2: DESCRIPTION OF THE STUDIES INCLUDED

Author/year	Study design	Median/mean time of follow up	CML phase	Number of patients	Drug	Dose (mg)	Dose schedule
Kantarjian *et al.*, 2009a	RCT	26 months (6,9 - 32,7)	CP	101	Dasatinib	70 mg	bid
				49	Imatinib	400 mg	bid
Shah *et al.*, 2010	RCT	22 months (<1 - 31)	CP	167	Dasatinib	50 mg	bid
				167	Dasatinib	70 mg	bid
				165	Dasatinib	100 mg	qid
				163	Dasatinib	140 mg	qid
Kantarjian *et al.*, 2009b	RCT	15 months (0,16 - 34,5)	AP	157	Dasatinib	70 mg	bid
				157	Dasatinib	140 mg	qid
Saglio *et al.*, 2010	RCT	2 years	BC – MBP	74	Dasatinib	70 mg	bid
				74	Dasatinib	140 mg	qid
			BC – LBP	33	Dasatinib	70 mg	bid
				28	Dasatinib	140 mg	qid
Hochhaus *et al.*, 2008	NRCT	15,2 months (1 - 18,4)	CP	387	Dasatinib	70 mg	bid
Apperley *et al.*, 2009	NRCT	14,1 months (0,1 - 21,7)	AP	174	Dasatinib	70 mg	bid
Cortes *et al.*, 2008	NRCT	12 months (0,03 - 20,7)	BC – MBP	109	Dasatinib	70 mg	bid
			BC – LBP	48	Dasatinib	70 mg	bid
Sakamaki *et al.*, 2009	NRCT	24 weeks	CP	12	Dasatinib	70 mg	bid
		12 weeks	AP and BC	11	Dasatinib	70 mg	bid
Schmidt *et al.*, 2010	PC	20 months	Not specified	7	Dasatinib	Not specified	Not specified
Klamova *et al.*, 2010	PC	8 months	CP	41	Dasatinib	100 mg	qid
			AP and BC	23	Dasatinib	140 mg	qid
Garg *et al.*, 2010	PC	16 months (3 - 34)	All phases	7	Dasatinib	70 mg	Bid

				3	(second line)	50 mg	bid
				2		100 mg	qid
				1		180 mg	qid
				1		50 mg	qid
				15	Dasatinib (third line)	70 mg	bid
				5		50 mg	bid
				1		120 mg	bid
				9		100 mg	qid
				3		140 mg	qid
				1		50 mg	qid

* Qid: once daily; Bid: twice a day; MBP: myeloid blast phase; LBP: lymphoid blast phase

1. **Pharmacotherapy follow up:** No pharmacotherapy follow up method has been identified, neither in clinical trial nor in prospective cohorts, and it hasn't been applied in patients with CML using dasatinib.

2. Patients follow up:

a. **Patient baseline evaluation:** To first evaluate CML patients in use of dasatinib, all studies proposed distinct evaluation assessments. BCR-ABL point mutations were analysed for all studies except Apperley *et al*., 2009 at baseline. First evaluation of hematologic parameters as complete blood counts was described in four studies, 23-26 bone marrow aspirates/biopsies also for four 23, 25-27 and quantitation of BCR-ABL gene transcript level for four. 25-28 Physical examination was performed for two studies. 25, 29 Apperley et al., 2009 also assess patients' performance status, vital signs and 12-lead electrocardiogram.

b. **Patient efficacy assessment:** All studies performed at least one of the standard parameter as complete blood counts, bone marrow biopsy or aspirate and quantitation of BCR-ABL gene transcript levels to assess hematologic, cytogenetic and molecular responses, respectively.

The hematologic responses were assessed weekly, at least for the first 4 weeks, in all NRCT and RCT trials. After this primary period, the frequency changes in accordance with each study protocol (**Table 3**). In PCs, no standard frequency was identified.

Bone marrow biopsy or aspirate and quantitation of BCR-ABL gene transcript levels frequencies were not homogenous, even in the first year of dasatinib treatment. The interval of monitoring their responses may vary among one month to one year.

Kantarjian *et al*, 2009a was the only trial, which perform BCR-ABL point mutation analysis as an evaluation parameter of molecular response instead of quantitation of BCR-ABL gene transcript levels.

TABLE 3: STUDIES FREQUENCIES OF HEMATOLOGIC, CYTOGENETIC AND MOLECULAR ASSESSMENTS

	Complete blood counts	Bone marrow aspirates/ biopsies	Quantitation of BCR-ABL gene transcripts level	BCR-ABL point mutation analisys
RANDOMIZED CLINICAL TRIALS				
Kantarjian et al, 2009a	Weekly (first 12 weeks) then every 2 months.	Every 12 weeks.	Every 4 weeks (first 12 weeks) then every 3 months.	No description
Shah et al, 2010	Weekly (first 12 weeks) then every 3 months.	Every 12 weeks.	No description	No description
Kantarjian et al, 2009b	Weekly (first 6 weeks); week 8 and 12; then monthly.	Within 4 weeks and then at the end of the months 1,2,3,6,9 and 12.	No description	At the end of the treatment
Saglio e al, 2010	Weekly (first 20 weeks); monthly (first year); then every 3 months.	Months 1,2,3,6,9 e 12 and then every 6 months.	No description	No description

NON-RANDOMIZED CLINICAL TRIALS					
	Hochhaus et al, 2008	Weekly (first 12 weeks) then every 3 months.	Every 12 weeks.	Monthly	No description
	Apperley et al, 2009	Weekly (first 4 weeks)	Monthly (first 3 months) then every 3 months.	No description	No description
	Cortes et al, 2008	Weekly	Monthly (first 3 months) then every 3 months.	Monthly	No description
	Sakamaki et al, 2009	Weekly (first 4 weeks) then monthly .	12 weeks for AP-LMC patients * 24 weeks for BP-LMC patients.	12 weeks for AP-LMC patients * 24 weeks for BP-LMC patients.	No description
PROSPECTIVE COHORTS					
	Garg et al, 2009	Every 3 months	Every 3 months	Every 3 months	No description
	Klamova et al, 2010	Month 3 and 6 , every 6 months until reach CCyR and every 12 months thereafter	Every 3 months until MMR and at least every 6 months	Every 3 months until MMR and at least every 6 months	No description
	Schmidt et al, 2010	Every 2 weeks until reach CCyR and every 3 months thereafter	Every 6 months until MMR and every 12 months thereafter	Every 3 months until a negative response	In case of failure, suboptimal response or transcript level increase.

* CCyR: Complete cytogenetic response; MMR: Major molecular response.

c. **Patient evaluation for safety:** Only four studies described the assessments performed for patient safety. Physical examination was mainly employed, conducted for three NRCTs. 28-30 Apperley et al., 2009 also preconized patient's performance status, vital signs and follow up visits; Cortes et al., 2008 evaluated skin and mucosas and Shah et al., 2010 performed chest x-ray as assessment for safety.

d. **Patient loss of response:** The loss of response definition depends on the patients' phase of leukemia and the standard protocol chooses to be followed. Except for one PC study, Klamova et al., 2010, without description of disease progression management, the standard protocol to who have loss of response was dose escalation, treatment change to another TKI and treatment discontinuation whether the disease progress despite dose escalation.

e. **Other medication:** Five trials allowed the use of hydroxyurea, 11, 28-31 and three of them also the use of anagrelide 28-30 for treatment of elevated white blood cell counts and platelet counts, respectively. Usage was limited to two weeks.

f. **Adverse drug reaction management:**

i. **Hematologic toxicity:** Hematologic toxicity grade ≥ III; Three trials reduced dose or interrupted the treatment, whether any hematologic toxicity grade ≥ III, until the blood counts return to baseline.11, 28, 29 One trial, Kantarjian et al, 2009 A, with CML patients in AP or BC, interrupted the treatment or performed treatment change to imatinib 600 mg. Other two trials performed dose reductions,23, 27 and treatment interruption, 23 but do not established criteria for restarting treatment with the full dose.

Three trials followed the further management protocol for neutropenia grade IV: dose reductions or interruption due to hematologic toxicity were only considered after 14 days of treatment for patients with grade IV neutropenia (absolute neutrophil count [ANC] 0.5x109/L [500/mm3]). Bone marrow aspirate and biopsy were performed, and if marrow cellularity was less than 10%, treatment was interrupted until ANC was greater than 1.0x109/L (1000/mm3); treatment was interrupted regardless of biopsy results if grade IV neutropenia persisted for 4 weeks. Treatment was reinitiated at the original

dose for the first event and at a lower dose level for recurring events. If grade IV neutropenia occurred for a fourth time a decision on further dose reductions or discontinuation was made by the investigator and sponsor [24, 29, 30].

Leukocytopenia, anemia and thrombocytopenia (regardless of grade). The administration of myeloid growth factors and recombinant erythropoietin were permitted at the discretion of the investigator in four trials [11, 23, 28, 30], as well as transfusions of packed red blood cells and platelets, performed in one, Kantarjian et al., 2009a and three trials, [11, 23, 31] respectively.

ii. **Non-hematologic toxicity**: Non-hematologic toxicity ≥ grade II; For non-hematologic toxicities considered to be at least possibly related to dasatinib, dose reduction or treatment interruption were the recommendations of seven trials [11, 23, 24, 28-31]. Four of them described further details of this AE management: treatment was interrupted until recovery to no greater than grade 1 or baseline levels. Treatment was reinitiated at the original dose for the first grade 2 event but reduced by one dose level for a recurrence of the same event and reduced by a second dose level for a further recurrence [24, 28-30].

Two trials also defined that patients experiencing grade 3 or higher organ toxicity (eg, renal, cardiac, central nervous system) judge to be related to dasatinib or QTc interval of 530 msec or longer were taken off therapy [24, 30].

Furthermore, one trial permitted treatment crossover to imatinib 800 mg. [31]

Pleural effusion: Seven studies endorsed the strategy of dose reduction, treatment interruption, diuretics and/or pulse steroid therapy [11, 25, 27-31].

Apperley *et al*., 2009 also preconized chest x-ray, with or without chest computed tomography, at the investigator's discretion, after occurrence of respiratory symptoms.

Bleedings or hemorrhages: Two trials recommended treatment interruption, dose reduction or treatment discontinuation with any sign of bleeding or hemorrhage of any grade [11, 28].

Intolerable toxicity: Whether toxicity due dasatinib was considered intolerable, all trials discontinued the treatment.

3. **Adverse drug reaction:** In this section, data from ADR grades III and IV was described by type (hematologic and non-hematologic) and CML phases. Except for one NRCT, Sakamaki et al., 2009 and one PC, Schmidt et al., 2010, due to the fact that the ADR results presented did not have distinction data between CML and Ph+ ALL populations or even between CML phases and lack of information of each drug therapy patients were into, respectively.

a. **Hematologic:** Hematologic ADR grade III and IV identified in CT are described in **Table 4**/

TABLE 4: DESCRIPTION OF GRADES III AND IV HEMATOLOGIC DRUG REACTION DATA, PRESENTED IN PERCENTAGE, IN RCT AND NRCT

CHRONIC PHASE					
		Anemia	Leukocytopenia	Neutropenia	Thrombocytopenia
Hochhaus et al, 2008	70 mg bid	21,5%	26,9%	48,9%	48,4%
Kantarjian et al, 2009A	70 mg bid	20%	24%	63%	57%
Shah et al, 2010	100 mg qid	13%	18%	35%	23%
	70 mg bid	18%	24%	45%	38%
	140 mg qid	19%	22%	44%	41%
	50 mg bid	18%	27%	47%	36%
ACCELERATED PHASE					
Apperley et al, 2009	70 mg bid	69%	59%	76%	82%
Kantarjian et al, 2009B	140 mg qid	48%	*45%*	59%	64%
	70 mg bid	43%	67%	69%	41%
BLAST PHASE					
Cortes et al, 2008	70 mg bid – MBP	69%	61%	80%	82%

	70 mg bid – LBP	50%	71%	81%	88%
Saglio et al, 2010	140 mg qid – MBP	76%	61%	79%	81%
	70 mg bid – MBP	78%	60%	74%	80%
	140 mg qid – LBP	52%	79%	79%	85%
	70 mg bid – LBP	50%	71%	81%	88%

QID: once daily; BID: twice a day; MBP: myeloid blast phase; LBP: lymphoid blast phase.

Hematologic ADR grade III and IV identified in PC are described below.

Garg *et al.,* 2009 discontinued treatment of 2 patients, who were receiving dasatinib as second line therapy, due to thrombocytopenia and one patient, receiving dasatinib as third line, because of neutropenia, despite an acceptable response [32].

Klamova *et al., 2010* registered, in CP, hematologic toxicity grade III and IV neutropenia and thrombocytopenia in 28% (11/41) of patients and in AP, in 62% (14/23) of patients.

b. **Non-hematologic:** Non-hematologic ADR grade III and IV identified in CT are described in **Table 5**.

Table 5. Description of the non-hematologic drug reaction grade III and IV data > 3% in RCT and CT.

	CHRONIC PHASE						ACCELERATED PHASE			BLAST CRISIS					
	Hochhaus et al, 2008	*Kantarjian et al, 2009*	*Shah et al., 2010*				*Apperley et al, 2009*	*Kantarjian et al, 2009*		*Cortes et al, 2008*		*Saglio et al, 2010*			
	70 mg bid	70 mg bid	100 mg qid	140 mg qid	70 mg bid	50 mg bid	70 mg bid	140 mg qid	70 mg bid	70 mg bid MBP	70 mg bid LBP	140 mg qid MBP	70 mg bid MBP	140 mg qid LBP	70 mg bid LBP
Nonhematologic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Diarrea	11 (2,8)	3 (3)	2 (1)	7 (4)	6 (4)	4 (2)	13 (8)	4 (3)	5 (3)	8 (7)	1 (2)	4 (5)	2 (3)	0 (0)	2 (7)
Nausea	3 (0,8)	0	1 (1)	1 (1)	1 (1)	1 (1)	1 (<1)	1 (1)	3 (2)	4 (4)	0 (0)	1 (1)	0 (0)	1 (3)	1 (4)
Vomiting	2 (0,5)	0	1 (1)	0 (0)	2 (1)	2 (1)	4 (2)	1 (1)	2 (1)	3 (3)	1 (2)	-	-	-	-
Headache	4 (1)	2 (2)	1 (1)	5 (3)	3 (2)	0 (0)	1 (<1)	2 (1)	1 (1)	2 (2)	1 (2)	1(1)	1 (1)	1 (3)	2 (7)
Musculoskeletal pain	-	1 (1)	3 (2)	6 (4)	2 (1)	2 (1)	-	0 (0)	3 (2)	-	-	-	-	-	-
Fatigue	8 (2,1)	3 (3)	4 (2)	7 (4)	4 (2)	0 (0)	7 (4)	3 (2)	5 (3)	2 (2)	2 (4)	-	-	-	-
Superficial edema	-	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	-	-	-	-	-	0 (0)	2 (3)	0 (0)	0 (0)
Fluid retention	-	7 (7)	6 (4)	16 (10)	12 (7)	8 (5)	-	12 (8)	17 (11)	-	-	4 (5)	8 (11)	2 (6)	2 (7)
Other fluid retention	-	-	-	-	-	-	-	2 (1)	8 (5)	-	-	-	-	-	-
Pleural effusion	24 (6,2)	5 (5)	4 (2)	9 (5)	8 (5)	6 (4)	8 (5)	11 (7)	10 (6)	16 (15)	3 (6)	4 (5)	4 (5)	2 (6)	1 (4)
Dyspnea	20 (5,2)	5 (5)	3 (2)	8 (5)	11 (7)	10 (6)	7 (4)	5 (3)	11 (7)	7 (6)	1 (2)	-	-	-	-
Congestive heart failure	14 (4)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pericardial effusion	-	-	2 (1)	2 (1)	3 (3)	3 (2)	-	1 (1)	5 (3)	-	-	-	-	-	-
Febrile neutropenia	-	-	-	-	-	-	-	6 (4)	16 (10)	5 (5)	7 (15)	9 (12)	5 (7)	4 (12)	3 (11)
Bleeding	-	1 (1)	2 (1)	4 (2)	1 (1)	6 (4)	-	13 (8)	11 (7)	-	-	7 (9)	7 (9)	3 (9)	1 (4)
GI bleeding	-	-	1 (1)	3 (2)	0 (0)	5 (3)	-	9 (6)	10 (6)	6 (6)	0 (0)	5 (7)	6 (8)	1 (3)	0 (0)
CNS Bleeding	-	-	-	-	-	-	-	-	-	-	-	0 (0)	0	1 (3)	1 (4)
Other bleeding	-	-	2 (1)	1 (1)	1 (1)	1 (1)	-	3 (2)	2 (1)	-	-	2 (3)	1 (1)	1 (3)	0 (0)
Rash	2 (0,5)	0	3 (2)	3 (2)	1 (1)	2 (1)	2 (1)	0 (0)	1 (1)	0 (0)	2 (4)	1 (1)	0 (0)	0 (0)	0 (0)
Pyrexia	4 (1)	0	1 (1)	1 (1)	0	1 (1)	7 (4)	3 (2)	2 (1)	5 (5)	1 (2)	-	-	-	-
Infection	-	4 (4)	1 (1)	3 (2)	2 (1)	1 (1)	-	9 (6)	3 (2)	-	-	-	-	-	-

Another ADR grade III or IV observed in these trials, with proportion lower than 3%, were anorexia, abdominal pain, asthenia, peripheral edema, superficial edema, pulmonary edema, pulmonary hypertension, inflammation/infection of superior respiratory tract, cough, arrhythmias, cardiac dysfunction, CNS bleeding, epistaxis, pruritus, petechiae and constipation.

Non-hematologic ADR grade III and IV identified in PC are described below.

Garg *et al*., 2009 took off 3 patients (21,6%), who were receiving dasatinib as second line therapy, due of non hematologic intolerance (pleural effusion in 2 patients and protein-losing enteropathy in 1) and 2 patients, receiving dasatinib as third line, who discontinued because of pleural effusion, and 1 each for gastrointestinal bleeding, renal failure, atrial fibrillation, and myalgias.

Klamova *et al.,* 2010 registered in CP patients non-hematologic toxicity grade III and IV in 7% (3/41) of patients; pleural effusion appeared in 2 patients and, in AP, in 33% (8/23) of patients.

DISCUSSION: The implementation of TKIs as therapy for CML has completely changed expectations about the disease prognosis. Increasing patient's survival time required a reassessment of care methods in monitoring and follows up of patients. Once the TKI dasatinib is the second-line treatment, there has been, consequently, a previous failure or intolerance to imatinib, increasing even more the attention that these patients should have to these parameters.

The analysis of search results shows that there is literature available containing monitoring follow up and ADR data specific to CML patients treated with dasatinib. However, there is not for pharmacotherapy follow up method.

Regarding to the search methotology applied to this systematic review, it was appropriated to identify the two follow up methods because it was done with the broad terms "dasatinib" and "chronic myeloid leukemia". Therefore whether there were any comparative studies of pharmacotherapy follow up methods/programs or of pharmacist participation referring to this specific illness and drug treatment, that search would have found.

At baseline assessments, it was possible to observe the importance of screening for new mutations. Acquired genetic mutations in the BCR-ABL domain also are interconnected with the route and treatment outcomes [33]. This analysis allows direct the patient to appropriate second-line treatment.

Concerning the efficacy assessments, bone marrow biopsy or aspirate was performed more frequently in studies in which AP-CML or BC-CML patients were treated (usually monthly in the first three months). That can be explained due to disease progression on the later phases is defined on a shorter period of time (progression was defined as no decrease from baseline levels in percentage of blast in PB or BM on all assessments of a 4 week period after receiving the maximum dose of dasatinib) [29].

Assessments of patient safety have been poorly described in most studies, even though they are essential for the monitoring follow up in order to early detect and prevent ADR and others drug-related problems. For safety, it would be important to highlight points as the establishment of physical examinations and chest X-ray for the prevention of pleural effusion.

Due to the high cost of treatment, monitoring response and safety with frequent assessments (even wheter they are also expensive) allows the early detection of treatment failure or intolerance, promoting an action (treatment discontinuation or change) that results in an increase in the cost-effectiveness of a treatment properly monitored.

The management of severe ADR proved to be well established and structured for both hematological and non-hematological ADRs. The currently ADR grade III and IV description was in accordance with the already published data [34]. It is possible to observe higher rates of hematologic ADR in the later phases of CML not related with the dose and schedule, which neutropenia and thrombocytopenia were the ones more frequent.

Dasatinib was associated with a greater degree of myelosuppression, in particular thrombocytopenia. In BC phase, that rates were similar to those reported at 8 months and 1 year's follow up, suggesting that most of the myelosuppression occurs early during the course of therapy [30]. This is consistently what occurs with other tyrosine kinase inhibitors, where most cytopenias are observed during the first few months of therapy. The greater potency of dasatinib may contribute to this more profound myelosuppression attributable to rapid clearance of BCR-ABL expressing malignant hematopoietic cells [31].

The non-hematologic ADR vomiting, fatigue, fluid retention, dyspnea, bleeding, GI bleeding and pyrexia were observed in patients in all three phases of CML.

In the chronic phase (considering any dose) it is observed fluid retention, dyspnea and pleural effusion as severe reactions more frequent. The ADR profile remains the same comparing 140 mg with 100 mg diary dose; however patients that received the 100 mg dose presented less AEs treatment-related (ie, cytopenia and pleural effusion), becoming the recommended doses based upon that results and the non-inferior cytogenetic response rates, estimated progression free-survival and estimated overall survival, despite the lower intended total dose [10, 11].

In accelerated phase, the ADR profile changes, highlighting the higher occurrence of bleeding and gastrointestinal bleeding. Furthermore, in blast crisis, febrile neutropenia, follow by bleeding and fluid retention were the ADR more observed.

It is noteworthy that there are differences in the profiles of patient` ADR depending on the CML phase, therefore personalized support and patient education is an essential tool in the safety of treatment.

The implementation of a patients follow up method is crucial to qualify the assistance and standardize the conducts, as this systematic review shows, there are data available to consultation.

Despite the need for increased patient education regarding oral chemotherapy and processes to monitor adherence and adverse events, none study have described any applied method regarding education or monitoring this parameters in CML patients receiving dasatinib. Neither the importance of a standard method of pharmacotherapy follows up performed by a health care professional, as a pharmacist.

The pharmacist in this scenario must give clear instruction to the patients on how and when to take their medications. Each patient should be guided to successfully incorporate the medications into his or her personal routines and schedules. Besides during the initial workup for CML and at each follow up visit after initiation of therapy, the pharmacist has many opportunities to educate patients and foster a strong patient-practitioner relationship. Patient education regarding treatment and symptom management is a vital aspect of caring for the patient with CML.

Because of the risk of severe adverse effects in this treatment, standardizing care in settings where chemotherapy is delivered is essential [35]. Patients should be educated to report symptoms, for example, chest pain, dyspnea, and dry cough as soon as they occur. It is essential that patients understand the importance of report symptoms in a timely manner.

Potential drug interactions with TKI also must be discussed in-depth so that all medications are taken into account, even over-the-counter medications, herbal supplements and dietary interactions.

Studies which performed and evaluated pharmacotherapy follow up methods in patients with chronic diseases as hypertension 36, diabetes type II [37, 38], cardiovascular risk [19, 39] showed an improvement in patients outcomes and considered that the pharmacotherapy follow up method conducted by pharmacists can play an important role in the achievement of therapeutic goals.

Considering studies relating pharmacotherapy follow up with cancer patients, Liekweg *et al.,* 2012 in a prospective, multicentered cohort study with a control group, explore the feasibility and potential of pharmaceutical care for breast and ovarian cancer patients treated in outpatients settings.

They measured patients-reported outcomes and showed that patient satisfaction with information was significantly higher in the intervention group, as well as quality of life and response to the antiemetic prophylaxis which demonstrated to be statistically significant higher (35,4% in the control group and 76% in the intervention group; $p<0,001$) [40].

Simons *et al*, 2011 in a prospective multi-centre observational cohort study investigated the effect of an intensified multidisciplinary pharmaceutical care programme on the adherence of cancer patients treated with capecitabine. Patients in the intervention group received a combination of written and spoken information; the characteristics of the drug capecitabine, including mechanism of action, possible adverse events and their appropriate management, as

well as the individual treatment regimen were explained in detail.

Furthermore, patients were informed about the importance of a high adherence to this drug and the risks of inadequate compliant behaviour. Patients were also educated about any other additional medication they were taking. Patients received a leaflet with information about the prevention and management of adverse effects of chemotherapy. They were contacted at least once during each cycle of capecitabine chemotherapy to inquire about any current therapy-related questions or problems and to reconfirm the ongoing individual therapeutic regimen.

This group exhibited an enhanced but not significantly different mean overall adherence compared to the control group (97.9% vs 90.5%, p=0.069). Mean daily adherence was significantly higher in the intervention group (96.8% vs 87.2%, p=0.029). Variability of both adherence parameters was considerably reduced when pharmaceutical care was provided. At the end of the observation period of 126 days, the probability of still being treated with capecitabine was found to be 48% in the control group and 83% in the intervention group (p=0.019, log-rank test) [41].

Whereas Escudier *et al.,* 2012 presents a perspective on multidisciplinary management of metastatic renal cell carcinoma. Oncology pharmacists have a duty to safely prepare and accurately dispense oncology drugs; the hospital pharmacist offers expert knowledge of drug interactions at the prescribing stage and during long-term treatment. Pharmacists may contribute towards the effective management of cancer-related pain, nausea and emesis. In relation to targeted agents, they have a potential role in informing patients about the prevention of toxicities and in advising on their management [42].

In a handsearch for pharmacotherapy follow up methods in chonic myeloid leukemia no studies, even with imatinib mesylate, describing the performace of a pharmacotherapy follow up method were found. Although, there is one study by Moreira *et al,* 2009, which suggest a methodological approach model of pharmacotherapeutical follow up in chronic myeloid leukemia in treatment with imatinib mesylate. However, we do not identify studies of application and validation of the proposed method [43].

Therefore, the presence of a pharmacist and a pharmacotherapy follow up method must be incorporated in this new role of long-term CML treatment with dasatinib in order to rationalize resources, increase the efficacy and safety of the treatment and improve the adherence and life's quality of the patient.

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