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Review Article

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Imatinib Efficacy, Safety and Resistance in Iranian Patients with Chronic Myeloid Leukemia: A Review of Literature

Asiyeh Amouei[1], Nesa Daeian[1], Seyedeh Sana Khezrnia[1], Ava Mansouri[1], Molouk Hadjibabaie[2]

[1]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author: Ava Mansouri**,** Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88814157
Email: ava_mansouri_j@yahoo.com

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ABSTRACT

Background: Imatinib is the gold standard in the treatment of chronic myeloid leukemia (CML) patients. Resistance to imatinib is interfering with patients' responses and their survivals.

Materials and Methods: We designed a systematic search to find relevant studies by applying appropriate keywords in PubMed, Web of science, Scopus, Ovid, ProQuest, Science direct and Google scholar for English studies. We also investigated the aforementioned terms' correspondence in Magiran, Scientific information database (SID) and Google scholar for Persian articles.

Results: 25 studies were selected for final analysis. Reported hematologic responses from adult studies ranged 86-99% and major molecular responses were estimated in 38.84% of our patients within 12 months of treatment. The most frequent reported adverse drug reactions (ADRs) were edema (n=5 studies, 100%) and fatigue and nausea (n=4 studies, 80%); ADR per capita ratio was 1.46. Only one study informed ADRs in pediatrics demonstrating 93% of patients experienced ADRs after receiving imatinib. Most of the Studies (n=4, 67% from 7 studies) considered BCR/ABL point mutation as main reason of imatinib resistance. Drug-binding site and P-loop regions were two common sites for BCR/ABL point mutation.

Conclusion: Imatinib as the first line treatment for CML has been associated with proper and durable responses in Iranian adults and children CML patients. Moreover, Imatinib life-threatening adverse effects were reported uncommon. Various responses to modified regimens have been reported in resistant patients; therefore, individualized treatment based on mutation type could be recommended.

Keywords: Imatinib mesylate; Treatment outcome; Antineoplastic agent resistance; Chronic myeloid leukemia; Adverse drug event

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal disorder of hematopoietic cells that is identified by Philadelphia chromosome as a result of reciprocal translocation between chromosomes 9 and 22, t (9; 22) (q34; q11)[1] which leads to BCR/ABL chimeric gene[2]. The BCR/ABL gene encodes an oncoprotein, a constitutive active tyrosine kinase, which enhances cell proliferation and apoptosis inhibition by stimulating several signaling pathways, leading to overgrowth of leukemic cells and CML [3, 4].

Imatinib Mesylate is the first tyrosine kinase inhibitor (TKI) that was introduced in 2001 for clinical practice in CML patients[5]. It induces apoptosis and inhibits proliferation in BCR/ABL–expressing cells through competitive blockage of ATP binding to BCR/ABL tyrosine kinase[6]. Imatinib is the first line treatment in CML patients[7], which leads to proper responses as

82% complete cytogenetic response (CCyR), overall survival (OS) rate of 86%, event-free survival (EFS) rate of 81% and 93% transformation-free survival at 7 years [8, 9].

The rate of imatinib resistance is estimated 4% per year from a 5-year follow up evaluation[10], which is higher in advanced disease stages. For instance, in Accelerated Phase-CML (AP-CML), imatinib resistance is 45% and 75% after 2 and 4 years of imatinib therapy, respectively [2].

Second-generation of TKIs, dasatinib (in 2006) and nilotinib (in 2007) initially were developed for imatinib resistant and/or intolerant patients. Following increased response rate and decreased disease progression, FDA approved new TKIs as frontline CML therapy in 2010 [11, 12]. Despite the superiority of these new TKIs in some aspects, review of the literatures indicates that imatinib still has an acceptable efficacy and safety profile in the treatment of CML[13,14]. In addition, the price of the Second-generation of TKIs is extremely higher than imatinib. Therefore, imatinib still is the first line treatment of CML in many Asian countries as well as Iran [15,16].

Since regional differences in biologic, environment and socioeconomic factors, the type and source of consumed imatinib and even patients' genetic background impacts on the treatment outcomes, it is essential for each region or country to precisely evaluate the rationality of the practice based on their population studies. Therefore, we decided to review the available evidence from Iran to assess if it supports imatinib therapy as first line treatment in Iranian CML patients. This paper reviews all available studies on imatinib efficacy, safety and resistance in Iranian children and adult patients.

MATERIALS AND METHODS

Data Sources and Searched Terms

In order to review available literature on imatinib efficacy, safety and resistance in Iranian CML patients, we accomplished a systematic search using different databases and publishers search engines. We searched PubMed, Web of science, Scopus, Ovid, ProQuest, Science direct and Google scholar for English studies. Likewise, Magiran, Scientific information database (SID) and Google scholar were investigated for Persian articles.

We performed our search using ("imatinib" OR "gleevec" OR "glivec" OR "imatinib as MeSH") AND ("Iran" OR "Iranian" OR" I.R.Iran") and their corresponding Persian equivalents within the title, abstract, keywords or MeSH based on search engines characteristics. Limitations and filters were supposed to be applied only if we encountered with various irrelevant results.

Afterward, we also manually searched references within relevant articles with the intention to avoid omitting any proper study. The search time span was up to October 2019.

Inclusion and Exclusion Criteria

We included all original, population based studies on Iranian adults and children CML patients with any extractable information about imatinib efficacy and/or adverse effects and/or resistance; i.e., clinical trials, longitudinal, cohort, cross-sectional, case-series and case-control studies. Hence, letters, case reports, conference papers, organizational reports, opinions or editorial papers were eliminated. Furthermore, case reports that described new imatinib adverse events were remained.

We also excluded publications which contained studies on cell lines and animal models likewise studies that investigated outcomes of gastrointestinal stromal tumor (GIST) patients.

Selecting Studies

We imported all search results to Endnote X8 library. After removing duplicated studies, two authors independently reviewed the remained articles through titles and abstracts screening and irrelevant studies were eliminated according to aforementioned inclusion and exclusion criteria. Full texts were assessed in case the title or abstract were not informative enough.

Information extraction and Reporting

We extracted and summarized the applicable data, which was reported in the most recruited articles in four Tables. These data were summarized and completed for each article based on the listed characteristics in 4 Tables:

Table 1:

- Study characteristics [Authors' name/ publication year, time of research, study design, comparison arms]
- Patients characteristics [patient's age group, sex, range of age]
- Disease and treatment characteristics [disease phase, treatments before imatinib therapy, imatinib type and initial dose, duration of imatinib therapy]
- Follow-up characteristics [treatment modification and its cause, response after treatment modification, follow up duration]

Table 2:

- Efficacy profiles [types of response (hematologic, molecular, cytogenetic and none), OS, progression-free survival (PFS), frequency of disease progression and its reasons, mortality rate and its causes]

Table 3:

- Resistance characteristics [type of resistance, disease phase in mutated patients, detection methods, name of evaluated genes, frequency of mutation site in BCR**/**ABL kinase domain, percentage of gene mutation frequency (number of gene mutation/total detected mutation*100), T315I mutation assessment, percentage of patients' mutation frequency (number of mutated patients/all resistant patients *100)]

Table 4:

- Adverse drug reactions (ADRs) [frequency of patients with ADRs (number of patients who experienced ADRs/total patients who received imatinib), severity of ADRs (based on Common Terminology Criteria for Adverse Events (CTCAE) as follow: Grades 1 and 2 are mild and moderate reactions, respectively which do not need intensive interventions. Grades 3 and 4 are severe AEs, which demand medical interventions. In grade 3, adverse events lead to medical therapy or hospitalization or prolongation of hospitalization and in grade 4, life-threating events require immediate significant therapeutic interventions.)]

We also reported the ADRs per capita which is estimated by dividing total number of ADRs occurrence to total number of included patients.

Table 1: Study, patients, disease, treatment and follow up characteristics of the reviewed articles

Patients characteristics				Disease and treatment characteristics					Follow-up characteristics			
Authors / Years	Age group	Sex (no.)	Age (range)	Patients' disease phase on IM (no.)[¥]	Treatment before IM therapy (no.)	Duration of IM therapy (range) month	IM brand	Initial dose[∞]	Treatment modification (no.)	Causes of treatment modification	Response after treatment modification	Follow up (months)
Bahoush Gr, *et al.*/2009 (20)	Children	F (8) M (6)	Median 9.5 (2.5-14)	CP (14)	NA[a]	Median 22.5 (2-30)	Glivec	300	two pts discontinued therapy	progression of the disease in one pt and adverse event in the other	Grade 3 or 4 neutropenia and thrombocytopenia noted in two pts on high-dose therapy/improved condition after discontinuation of therapy for two weeks	Median 16.5 Mean 22.5 (2-30)
Hamidieh AA, *et al.*/2013 (40)	Children	F (13) M (6)	Median 9.5 (2-16)	CP (19)	INF (9) HU (12)	Unlimited[b]	NA	260	IM dose escalation to 320 (12%)	-No CHR after 3 months or no MCyR after 12 months and at least if the pts relapsed within 3 months after attaining CHR	NA	Median 24 (14.4-100.8)
Navidi GR, *et al.*/2005 (17)	Adult	NA	NA	NA (17)	NA	NA	Gleevec	NA	NA	NA	NA	NA
Razmkhah F, *et al.*/2010 (31)	Adult	F (14) M (16)	Mean 47 (14-83)	CP (30)	IM 1st line	Mean 28.8 (7-66)	Imatib	200, 300, 400	NA	NA[c]	NA	NA
Valizadeh N /2011 (25)	Adult	M (1)	28	NA (1)	IM 1st line	12	NA	400	NA	NA	NA	NA
Jalaeikhoo H, *et al.*/2011 (37)	Adult	F (197) M (220)	Mean ± SD 40.9 ± 14.5	CP (417)	HU (NA)	NA	Indian brand	400	IM dose escalation to 600 (NA)	-Pts failed to achieve CHR within 3 months	NA	72
Moshfeghi K, *et al.*/2013 (19)	Adult	F (34) M (52)	Mean 60	CP (86)	NA	NA	Iranian & Indian brand	400	IM dose escalation to 800 (NA)	-Absence of appropriate treatment response	NA	6
Mozaheb Z, *et al.*/20	Adult	F (34) M (26)	Median 48 (13-80)	CP (49) AP (7)	HU ± INF (13)	NA	Generic imatinib	400	- IM dose escalation to 600-800 mg (10) IM dose reduction to 100-300 mg (5) - IM interruption (9)	- Inadequate efficacy or intolerability - unresponsive	After a median follow-up of 36 months from dose escalation,	Median 44 (8-115)

Patients characteristics				Disease and treatment characteristics					Follow-up characteristics				
Authors / Years	Age group	Sex (no.)	Age (range)	Patient's disease phase on IM (no.)[¥]	Treatment before IM therapy (no.)	Duration of IM therapy (range) month	IM brand	Initial dose[∞]	Treatment modification (no.)	Causes of treatment modification	Response after treatment modification	Follow up (months)
14 (26)				BP (2)	IM 1st line (47)					ness or severe toxicity	70% of them remained alive	
Golabchifar AA,*et al.*/2014 (21)	Adult	F (25) M (36)	Median 32 Mean± SD 35.5 ± 11.9 (17–67)	CP (61)	IM 1st line	(12-36)	NA	NA	NA	NA	NA	NA
Mohajeri E, *et al.*/2015 (22)	Adult	F (17) M (19)	Median 44 Mean± SD 43 ± 10 (19-63)	CP (36)	NA	NA	Imatib & Imatinib-Osveh	400	NA	NA	NA	NA
Salamizand H, *et al.*/2015 (27)	Adult	F (29) M (41)	Mean± SD 47.9 ± 13.2	CP (59) AP (11)	IM 1st line	Mean± SD 44.16 ± 23.16	Gleevec	400	IM dose escalation to 600 mg (14)	-Suboptimal response and failure to IM	NA	NA
Payandeh M, *et al.*/2015 (39)	Adult	F (27) M (27)	Mean± SD 45.7 ± 13.8 (23-78)	CP (54)	IM 1st line	6	Indian brand	400	NA	NA	NA	NA
Payandeh M, *et al.*/2015 (41)	Adult	F (42) M (43)	Mean ±SD 47.5 ± 14.5 (23-82)	CP (85)	IM 1st line	NA	NA	400	NA	NA	NA	NA
Rejali L, *et al.*/2015 (30)	Adult	F (14) M (25)	Mean 46 (22-70)	CP (NA) AP (NA) BP (NA)[d]	NA	0 to > 61	NA	400	-IM dose Escalation to 500 or 600 mg -Nilotinib or Dasatinib	-IM resistance	-Failure MR (25; 63.2) -Warning category (4; 10.2)	NA

Patients characteristics				Disease and treatment characteristics				Follow-up characteristics				
Authors / Years	Age group	Sex (no.)	Age (range)	Patients' disease phase on IM (no.)[¥]	Treatment before IM therapy (no.)	Duration of IM therapy (range) month	IM brand	Initial dose[∞]	Treatment modification (no.)	Causes of treatment modification	Response after treatment modification	Follow up (months)
Rostami G, *et al.*/2015 (38)	Adult	F (15) M (15)	Median 50 (32-70)	CP (30)	NA	Median 22 Mean± SD 24.9±11.06 (8 to 50)	NA	400	-IM dose Escalation to 600-800 mg (13) -Nilotinib (9) .	-Suboptimal response	-Optimal response (10; 26.3)[₱] -MMR (10;45.45) -No MMR (12;54.54) -Dead, two of three mutated pts[₱]	Median 23 (11-50)
Abbasian S, *et al.*/2015 (42)	Adult	F (20) M (28)	Mean 40 (15-46)	CP (48)	NA	24 to 96	NA	NA	NA	NA	NA	NA
Chahardouli B, *et al.*/2013 (23)	Adult	F (23) M (37)	Mean 44 (12-77)	CP (43) AP (4) BP (13)	IFN ± HU (25) IM 1st line (35)	NA	NA	NA	- IM dose escalation to 600-800 mg and then replacement with Nilotinib and Dasatinib (1) - Dasatinib and BMT (1)	-Absence of treatment response -Disease development to blastic phase	- Increased BCR/ABL copy numbers to %86.6 and peak of T315I mutation to 60% and finally death (1) - Relapse 3 months after HSCT and death (1)	NA
Chahardouli B, *et al.*/2013 (24)	Adult	F (43) M (67)	Median 42 (10-83)	CP (93) AP (4) BP (13)	IFN ± HU (25) IM 1st line (85)	≥ 6	NA	NA	-IM dose escalation to mg 600- 800	-Suboptimal response	NA	NA
Solali S, *et al.*/2013 (29)	NA	NA	NA	CP (16) AP (10) BP (4)	NA	NA	NA	NA	NA	NA	NA	NA
Nekoohesh L, *et al.*/2019 (36)	Adult	F (119) M (136)	Median 41.3 (18-84)	CP (255)	IM 1st line	NA	NA	400	NA	NA	NA	Median 34.8 (3-845)

	Patients characteristics			Disease and treatment characteristics				Follow-up characteristics				
Authors / Years	Age group	Sex (no.)	Age (range)	Patients' disease phase on IM (no.)¥	Treatment before IM therapy (no.)	Duration of IM therapy (range) month	IM brand	Initial dose∞	Treatment modification (no.)	Causes of treatment modification	Response after treatment modification	Follow up (months)
Payandeh M, *et al.*/2018 (35)	Adult	F (36) M (24)	Median 41 (21-80)	CP (60)	NA	Median 4 (1-10)	NA	400	NA	NA	NA	NA
Safaei A, *et al.*/2018 (28)	Adults and pediatrics	male:female ratio of 1.8:1).	Mean 44 (4-90)	CP (81.3%) AP (8.2%) BP (10.4%)	NA	NA	NA	NA	NA	NA	NA	NA
Vatanmakanian M, *et al.*/2019 (32)	Adult	F (11) M (9)	Median 49 (21-75)	CP (9) AP (5) BP (6)	NA	NA	NA	200-400 for CP 300-800 for AP 600-800 for BP	NA	NA	NA	11
Rostami G, *et al.*/2017 (33)	Adult	F (28) M (32)	Median 49 (17-81)	CP (60)	NA	Median 48 (3-142)	NA	400 or 800	NA	NA	NA	Median 49 (4-216)
Chahardouli B, *et al.*/2019 (18)	Adult	F (38%) M (62%)	21-82	NA	NA	18-60	NA	NA	NA	NA	NA	NA

[a]Patients excluded if they had received treatment with HU, INF-α or cytarabine and any other investigational agent within seven, 14 and 28 days, respectively before starting the study treatment. [b]It means that the patient should take the drug until the disease progressed or relapsed. [c]The dosage of Imatib was adjusted according to non-hematological and hematological toxicities. [d]A lot of information is missed.

pt(s): patient(s). ¥ total numbers of patient equal to all patients on imatinib therapy, ∞ imatinib dosing for adult mg/day and for children mg/m2/day, ₱ Number of patients/all included patients*100 ł Number of patients/number of mutated patients*100, NA; not available or not applicable, IM; imatinib mesylate, HSCT; Hematopoietic stem cell transplantation, CML; chronic myeloid leukemia, CP; chronic phase, AP; accelerated phase, BP; blastic phase, HU; hydroxyurea, INF; interferon, CHR; complete hematologic response, MCyR; Major cytogenetic response, MR; molecular response, MMR; major molecular response

Table 2: Imatinib efficacy in Iranian CML patients

	Authors/year	Response			Mortality- % (Cause)	Progression to AP or BP no. (%)	Overall Survival (%)	Time to event end points (%)
		HR (no, %)	MR (no, %)	CyR (no, %)				
Adult	Jalaeikhoo H, *et al.*/2011 (36)	413 (99)	NA	NA	7.4 (relapse, MI and car accident)	46 (11)	6-year OS (89)	6-year EFS (83)
	Mozaheb Z, *et al.*/2014 (26)	56 (94)	MR (28,46.8)	NA	6.67 (progressive disease)	8 (13.4)	4-year OS (65)	44-month EFS (65)
	Razmkhah F, *et al.*/2010 (31)	27 (90)	CMR (14,46.7) PMR (13,43.3) NMR (3,10) MMR (44.1, 52.97 and 60.75%) at 12, 18 and 24 months	NA	NA	NA	NA	NA
	Payandeh M, *et al.*/2015 (71)	NA	NA	NA	NA	NA	5-year OS (90.5)	NA
	Moshfeghi K, *et al.*/2013 (19)	Iranian brand: 86% Indian brand: 86%	Iranian brand: 46.5% Indian brand: 44.2%	NA	NA	NA	NA	NA
	Golabchifar AA, *et al.*/2014 (21)	NA	MMR (31, 51.7)	CCyR (8,13.3)	NA	NA	NA	NA
	Salamizand H, *et al.*/2015 (27)	63 (90)	NA	CyR (49,70)	NA	NA	NA	NA
	Nekoohesh L, *et al.*/2019 (35)	NA	MMR (15.38, 25.18, 44.1,52.97,60.75) at 3, 6, 12, 18, and 24 months	NA	NA	NA	NA [a]	NA [a]
	Payandeh M, *et al.*/2018 (34)	NA	EMR (40%) MMR (28.33%) DMR (15%) CMR (16.67%) at 12 months	NA	NA	NA	NA	NA
	Vatanmakanian M, *et al.*/2019 (32)	CHR (88.8% in CP pts) at 6 months; (60% in AP pts) at 11 months; (50% in BP pts)	CMR (55.5% in CP pts) PMR (33.3% in CP pts) NMR (11.1% in CP pts) at 6 months; MMR (40% in AP pts) at 11 months; MMR (33.3% in BP pts) PMR (50% in BP pts) NMR (16.6% in BP pts)	NA	NA	NA	NA	NA
Pediatric	Rostami G, *et al.*/2017 (33)	NA	MMR (15 out of 25 pts with e13a2 transcript type; 30 out of 35 pts with e14a2 type) up to 24 months	CCRe (22 of the remaining 30 pts with *e14a2* transcripts; five of the remaining 15 pts with e13a2 transcripts) up to 12 months	NA	NA[b]	NA	NA
	Safaei A, *et al.*/2018 (28)	NA	MMR (72.5% of pts without ACA)	NA	NA	NA	NA[c]	NA
	Bahoush Gr, *et al.*/2009 (20)	Early CP: 7 (100) Late CP: 6 (85.7)	NA	CCyR (12,85.7) PCyR (1,7.1)	14.3 (progressive disease)	1 (7.15)	NA	30-month PFS (85.7)
	Hamidieh AA, *et al.*/2013 (39)	11 (57.9)	NA	CCyR (7,36.8)	21 (hematologic relapse and progressive disease)	8 (42.1)	2-year OS (87)	DFS (82)

[a]They are reported based on various BCR-ABL$_{IS}$ categories at different months. [b]One patient with *e13a2* and another one with *e14a2* transcript had disease progression within first 24 months of treatment. [c]Cum survival of 76 patients was calculated in this article: survival of patients with ACA; 49.7±11.1 months and survival of those without ACA; 77.3±3.1months. pt(s): patient(s). HR; hematologic response, CHR; complete hematologic response, NA; not available, CP; chronic phase, AP; accelerated phase, BP; blastic phase, MR; molecular response, EMR; early molecular response, MMR; major molecular response, DMR; deep molecular response, NMR; no molecular response, CMR; complete molecular response, ACA; additional cytogenetic aberrations, PMR; partial molecular response, CyR; cytogenetic response, CCyR; complete cytogenetic response, PCyR; partial cytogenetic response, CCRe; complete cytogenetic response equivalence, MI; myocardial infraction, OS; overall survival, EFS; event free survival, PFS; progression free survival, DFS; disease free survival

Table 3. Imatinib resistance characteristics in Iranian CML patients

Author(s) /Year	Type of resistance	Phases in mutated patients (no.)	Detection methods	Name of evaluated genes	T315I mutation assessment	Frequency of mutation site in BCR/ABL domain (%£)>10%	Gene mutation frequency(%£) >10%	Patients mutation frequency %ł
Rejali L, *et al.*/2015 (30)[a]	Secondary	AP (3) CP (1)	PCR-RFLP, DS	G250E L384M Y253H V379I	NA	P-loop (75) Between C- domain and A-loop (25).	G250E (25) L384M (25) Y253H (25) V379I (25)	10.25
Rostami G, *et al.*/2015 (38)	Primary Secondary	CP (3)	DS	E355G G398R	No mutation was observed	C-domain (66.66) A-loop (33.33)	E355G (66.66) G398R (33.33)	13.63
Abbasian S, *et al.*/2015 (42)	NA	NA	Real time-PCR	SIRT1 expression	NA	NA	NA	NA
Chahardouli B, *et al.* /2013 (23)	NA	AP (2) BP (2)	ASO-RT-PCR ,BDS	T315I	Mutation was observed	Drug-binding site	NA	7
Chahardouli B, *et al.*/2013 (24)	NA	CP (21) AP (3) BP (8)	BDS	G250E, T315I M244V, F359C E255K, M351T F359V, E459G Y253H, E255V D276N, E279A F317L, E355G L387M, L387F H396R, S438C E453A	Mutation was observed	Drug-binding site (29) P-loop (26) C-terminal (12)	G250E (14.7) T315I (11.8)	29.1
Solali S, *et al.*/2013 (29)	NA	NA	SYBER-Green Real-time RT-PCR	hOCT1 MDR1	NA	NA	NA	NA
Chahardouli B, *et al.*/2019 (18)	NA	NA	Real-time PCR	STAT3 expression	NA	NA	NA	NA

[a]The reported data in this article were ambiguous and confusing. £ number of gene mutations/total mutations*100, ł number of mutated patients/total resistant patients*100, NA; not available or not applicable, AP; accelerated phase, BP; blastic phase, CP; chronic phase, PCR; polymerase chain reaction, RFLP; restriction fragment length polymorphism, RT; reverse transcription, ASO; allele-specific oligonucleotide, DS; direct sequencing, BDS; bidirectional sequencing, hOCT1; human organic cation transporter, MDR1; multi-drug resistance 1, P-loop; phosphate-binding loop, A-loop; activation loop, C-terminal; carboxyl-terminal, C-domain; catalytic domain

Table 4: Frequency of imatinib adverse events

Adverse events	Grade 1 or 2-%	Grade 3 or 4-%
Edema€	1 (16), 56.4 (40), 62.7 (21), 55.6 (22), 42.8 (12), 22.3 (20)	7.3 (23), 7.4 (22)
Nausea	21.3 (40), 42.1 (21), 20.4 (22), 42.8 (12), 27.8 (20)	3.3 (40), 5.6 (22), 7.1 (12)
Vomiting	1.7 (40), 14.8 (22), 42.8 (12)	5.6 (22), 7.1 (12)
Myalgia	23 (40), 48.2 (22), 5.3 (14), 28.6 (12), 22.3 (20)	13 (22)
Musculoskeletal pain	37 (40), 57.1 (12)	3.6 (40)
Skin rash	28.3 (40), 5.3 (14), 16.7 (20)	6.6 (40)
Abdominal pain	39 (21), 18.5 (22), 21.4 (12), 33.4 (20)	9.2 (40)
Fatigue	43 (40), 43.8 (21), 30.5 (20)	-
Thrombocytopenia	1.4 (16), 13.3 (40), 10.45 (21)	3.3 (40)
Diarrhea	0.5 (16), 11.1 (22), 5.5 (20)	-
Arthralgia	10 (40), 50 (22), 5.3 (14), 28.6 (12)	11.1 (22)
Neutropenia	11.67 (40), 9.3 (21)	3.3 (40)
Ostealgia	35.2 (22), 5.3 (14)	13 (22)
Muscle cramps	37 (22), 21.4 (12)	20.4 (22)
Infection	5 (40), 16.7 (22)β	3.7 (22)β
Weight gain	18.5 (22), 57.1 (12)	-
Headache	39.5 (21), 25 (20)	-
Hemorrhagic events	17.6 (40)¥, 3.7 (22)	-
Anemia	66.7 (40)	3.3 (40)
Depression	24 (22)	5.6 (22)
Insomnia	22.2 (22)	14.8 (22)
Weight loss	20.4 (22)	1.85 (22)
Constipation	18.5 (22)	3.7 (22)
Cough	18.5 (22)	1.85 (22)
Fever	14.8 (22)	3.7 (22)
Pancytopenia	14.3 (12)	14.3 (12)
Pruritus	11.7 (40)	10 (40)
Liver toxicity	9.6 (40)	1.9 (40)
Dizziness	21.8 (40)	-
Dyspnea	14.3 (12)	-
Red eye	5 (40)	-
Urinary retention	1.85 (22)	-
Leukopenia	1.2 (16)	-

€ including peripheral, periorbital, superficial edema and fluid retention, β sinusitis and throat infection, ¥ including bleeding tendency and sub-conjunctival hemorrhage

DISCUSSION

We found that Iranian studies assessed imatinib effectiveness more than its safety and resistance. They were mostly performed in adults rather than children. Estimated median age of CML patients from European population-based registries ranged between 57-60 years, while it also stated that age of patients in clinical trials were 10 years lower [43]. The age of participants in our review ranged between 2 to 90 years. According to the studies reporting age, the age average and median of patients described 46.3 and 45.76, respectively, which are close to what Höglund *et al.* [43] stated about clinical trials.

In our review article, males were recruited 1.21 times more than females which is the same as what was reported previously (about 1.2-1.7) [43, 44]. These studies frequently recruited CP-CML patients and imatinib was often used as first-line therapy at dose of 400 mg. Despite existence discrepancies within reviewed studies regarding study design, participants, comparator groups, reporting different outcome measures, efficacy of imatinib was not noted inferior than comparator groups (e.g. HSCT) and developed acceptable responses in both adults and pediatrics. However, it should be considered that no study compared imatinib outcome to new TKIs generation such as nilotinib. Moreover, induced imatinib ADRs were often mild to moderate, and no death reported due to toxic effects.

Disease and treatment characteristics

Although imatinib is the drug of choice in CP of CML, other drugs such as interferon-α (IFN- α) and hydroxyurea (HU) have been prescribed for CML treatment. Two studies, both by Chahardouli *et al.*, reported the chemotherapy regimen before imatinib resistance occurrence. He reported that 41.7% [23] and 22.7%[24] patients were received HU plus IFN- α; however, imatinib was as the most prescribed first-line therapy as expected. This is also confirmed by studies other than our review article that about 20% of cases started drugs other than imatinib at first then they switched to imatinib after losing their response to the primary regimen [45, 46].

Imatinib resistance frequency is clinically important in guideline development, health regulatory and decision making. Despite the fact, only Rejali *et al*. [30] evaluated the frequency of imatinib resistance cases in Iranian CML population (39 resistant cases from 135 CML patients; 29 %).

Effectiveness and Safety of imatinib in adults

In 2010, FDA announced that second generation of TKIs (dasatinib and nilotinib) is suitable as choice of CML therapy due to their superior cost-effectiveness. Consequently since then, they became first-line treatment in some developed countries. However, from a different viewpoint by expiring Gleevec® patent in 2016 and releasing low-cost generic form of imatinib, it seems that imatinib also could be cost-effective and prescribed as first choice of treatment for many patients [47]. In Iran, the generic forms of imatinib are available. In comparison, nilotinib, the only existing second TKI generation in Iran, is accessible only as its original brand (Tasigna) that is much more expensive than generic imatinib despite being insured. Therefore, in Iran, like some other countries mostly developing ones imatinib is the drug of choice at the beginning of CML treatment based on Iran standard protocol [15]. Accordingly, in our studies, imatinib was mostly used as the first-line treatment (in some rare cases HU plus IFN- α were the 1st line treatment).

Also, we found Indian generic version of imatinib was mostly used in our studies. There are several reasons which can lead to this practice; 1) highly cost of Gleevec® which can be due to its high price and lack of national insurance coverage [37], 2) the physician beliefs in better quality of Indian generic vs. Iranian generic forms and 3) Inaccessibility of Iranian generic version of imatinib due to absence of their production inside the country during study periods (Iranian generic released in 2010 when the most studies had begun) [19].

Considering the CML different phases, imatinib was effective in all phases in our included studies which are in accordance with the review by Pulsipher *et al.* [48].

Imatinib efficacy in our included studies was reported by different response and outcome measures. The range for hematologic responses in our review was near to other adult studies [49, 50]. Only Moshfeghi *et al.* [19] reported hematologic responses less than other studies (86%). This can be explained by higher age of recruited patients since Sanchez-Guijo *et al.* confirmed that aging is associated with decrease in response [51].

Mean of MMR from our patients (38.84%) was better than what was reported in a systematic review (33.6%) in which 8 clinical studies were reviewed and compared relative efficacy of three TKIs [52].

The extracted OS and EFS from the current review proved durable imatinib consequence and were in accordance to IRIS trial [3,53]. Although Mozaheb *et al.*[26] reported lower rate for outcomes (65% for both OS and EFS), the difference could be due to the disease phase of Mozaheb *et al.* study population (patients were in AP and BP) based on previously lower PFS and OS rate of patients in AP-CML reported by Talpaz *et al.* [54].

One of our included studies [17] compared the effect of imatinib and hematopoietic stem cells transplantation (HSCT) by different measures; the percentage of BCR-ABL gene expression in several time points. The results showed that extent of gene expression after 8 months treatment statically was not different in both groups. Therefore, it was suggested that invasive techniques (HSCT) is better to be replaced with non-invasive methods (imatinib) at least in early disease phase.

Disease progression to AP or BP was reported to be the main cause of death in CML patients. Although in our studies there was a slightly higher percentage of progression [11, 50] (11-13.5% vs. 7), our mortality rate was lower (7% vs. 10-12%). The reason could not be clarified based on the reported findings in our studies. According to Rostami *et al.* study, *BCR-ABL1* transcript types can affect patients' response to imatinib. Patients with *e14a2* transcript had lower probability of recurrence, better and faster response to imatinib. Fifteen out of 25 patients with *e13a2* transcript type and 30 out of 35 patients with *e14a2* type achieved MMR up to 24 months[33].

ADRs due to imatinib therapy in CML patients have been reported to be mild to moderate and are mostly manageable [55]. In contrast with IRIS study in which 30% of patients experienced severe ADRs[37], the results of our studies supported acceptable safety profile of imatinib in Iranian CML patients according to its frequency and severity.

The calculated ADR per capita in our study (1.5) was lower than other studies (1.6 and 2.7) [3, 10]. In addition, the proportion of mild and moderate to severe and life threatening ADRs was higher compared to the only study in which its indicator was applicable (7.2 vs. 5.3)[3]. Hence, it seems imatinib induced less and lighter ADRs in Iranian patients.

In our included studies, as expected [3, 11, 53, 55, 56], the most common ADRs were reported to be edema (peripheral, per orbital and superficial). The other prevalent mild-moderate non hematologic ADRs were found to be fatigue, nausea, myalgia, abdominal pain, musculoskeletal pain, vomiting and skin rash. Some of these events are similarly reported in other studies, e.g. fatigue [11, 56, 57], nausea [10, 11, 55-58], muscle cramp [55-58], abdominal pain [11, 56, 57], skin rash [11, 56, 57], vomiting [10] and musculoskeletal pain [10, 56, 57]. Our frequent severe non-hematologic ADRs (grade 3-4) were skin rash as well as Kantarjian *et al*. study [55].

Despite the higher frequency of grade 3-4 for hematologic events (thrombocytopenia and neutropenia) in other studies [55,57-59], hematologic ADRs were not recorded among our frequent severe symptoms.

Effectiveness and Safety of imatinib in children

We encountered with the lack of evidence in Iranian pediatric CML patients due to inclusion of only three studies which evaluated imatinib efficacy in children[20,28,40]. Based on our knowledge, studies in which CML pediatrics were

considered are limited. It can be associated with infrequent risk of CML incidence in children population [57].

Two of our studies recruited patients who previously treated with other drugs such as HU. It could be due to enrolment of patients in these studies before FDA approval of imatinib pediatric use in 2003[60]. In contrast with others, the number of females was more in these studies [61, 62].

We faced with discrepancies in the responses of these studies. Hamidieh *et al*. [40] responses were very lower compared to Bahoush *et al*.[20] regarding CHR (58% vs. 93%, respectively) and CCyR (37% vs. 85.7%, respectively). Other studies on pediatrics reported range of CHR and CCyR 80-98% and 55-69%, respectively which are similar to Bahoush *et al.* results [60-63].

In addition, calculated mortality rate from the above-mentioned studies was lower than our results (14- 21% vs. 2- 4.5%); however, EFS and OS is compatible with our findings. These variations could be due to the stage of the disease that studies recruited their patients, genetic background, median participants' age or imatinib therapy timing (1st or 2nd line therapy). Although Bahoush *et al.* stated that there are no differences in patients' outcomes taking imatinib as first regimen or not, the sample size of their study was small (n=14, 2 groups of 7 patients). As we mentioned earlier, we are dealing with lack of evidence regarding Iranian pediatric imatinib efficacy which may alter our conclusion and lead to misconception.

Only one study reported detailed imatinib-induced adverse effects in pediatrics. Based on Bahoush *et al*. study [20], it seems that the total ADRs frequency in Iranian pediatric patients is high (93%).

In a review study by Suttorp *et al*. [60], similar ADRs to Iranian pediatrics were reported. They stated edema, nausea, vomiting and musculoskeletal pain as common ADRs based on different pediatrics studies which are in accordance with Bahoush *et al*. study [20].

There is paucity of studies regarding imatinib efficacy and safety in pediatric CML patients. However, our studies showed acceptable responses by children to imatinib and have not induced any fatal events. Therefore, imatinib therapy was suggested for CML children who are faced with absence of fully matched sibling donors.

Resistance characteristics

Imatinib resistance can happen through different pathways such as BCR/ABL gene expression or routes that decrease available imatinib concentration. But majority of imatinib resistance is due to gene mutation. So far, 50 mutation regions and more than70 particular mutations are recognized. It is suggested to evaluate the mutation in the case of imatinib resistance, prior to choosing the following treatment [64]. Accordingly, we found about 70% studies which detected BCR/ABL point mutation after resistance occurrence. This can remark the high frequency and also the importance of this mechanism in imatinib-resistance occurrence.

The mutation detection methods that were mostly applied by our studies are different types of PCR and direct sequencing. Kang *et al*. [65] confirmed that ASO-RT-PCR method is more sensitive, simple and faster than direct sequencing or PCR-RFLP methods. They suggested ASO-RT-PCR method for routine BCR/ABL mutations screening and direct sequencing for confirmation in positive cases. Chahardouli *et al.* [23] also detected mutation by ASO-RT-PCR in one of our included studies. They also reported *STAT3* gene as an effective target in the treatment of resistant CML patients [66].

Follow-up characteristics

The ABL1 KD mutations frequency was calculated 18.6 % (43/231 imatinib resistant patients) in four of our included studies. There are studies which reported more mutations in resistant patients like 32 mutations in 100 (32%) patients from Pakistan [67], 63% in Korean [46] and 58% in Chinese patients [68]. Among the reasons for these variations, we can point out 1) applying methods with different sensitivity such as direct sequencing and ASO-PCR, 2) inclusion of larger group of patients mostly in AP and BP, leading to

higher probability of detecting mutations and 3) the diversity of ethnic origins and genotypes.

Treatment modification is implemented according to the patient's condition and previous treatment. Our studies utilized high dose of imatinib 600- 800 mg per day or second or third generation TKIs for resistant or mutated patients, as suggested [69, 70].

Our included studies also followed the patients with modified regimen. These regimen modifications are supposed to be effective. It has been stated in the case of increasing imatinib dose, 50% of patients achieved the complete responses, and about 37.5% did not reflect any responses[67]. On the other hand, switching between the drugs within TKI group led to 41% complete *cytogenetic* response and 56% major cytogenetic response [71]. Although in our studies the authors did not make it clear that modifications outcomes were belonged to which groups (higher imatinib dose vs. next TKI generations), most of the patients could not achieve the proper responses or even lost former responses.

These discrepancies may be because of recruited resistant patients in order to assess the patient's outcomes from treatment modifications. Our studies mostly investigated imatinib resistant patients which were mutated and in all CP, AP and BP. While the other mentioned studies evaluated all resistant patients and only in CP [65, 70].

We found drug-binding site (T315I, etc.) and P-loop region as the most occurring mutations in resistant individuals. Kim *et al.* [46] revealed the incidence of mutation in P-loop and drug-binding site as 44% and 27% of total mutations in all three phases, respectively and T315I as the most common mutation. Also, in our review article, mutations mostly happened in advanced phases (AP or BP). These findings are the same as Nicolini *et al.* study [72]. They also suggested that these sites mutations lead to an inferior OS. Therefore, mutation sites can be another reason for poor responses in these populations.

Generally, SIRT1 and MDR1 expression are higher in resistant patients than in sensitive patients to imatinib. BCR/ABL gene mutation almost happens in drug-binding site or P-loop regions.

Escalating dose of imatinib or applying second or third generation TKIs have not led to proper responses in most patients in advanced phases or in whom which had particular mutations. So, it is suggested to perform the mutation screening prior choosing treatment strategy in the purpose of achieving optimal response and decreasing expenditures.

CONCLUSION

Although the included studies consisted of valuable information, this information was not beneficial in order to respond to some of our questions. Extracting data from these studies was difficult. Also, summing up their results was not convenient. These mainly were due to lack of quality in data reporting and the variation in evaluated characteristics. Some crucial characteristics were missing from one to another study, and they all did not cover equivalent information. Studies also varied in reporting denominators which makes it hard to track the whole situation. So, we need further studies with covering specific standard fields and identical reporting practices.

As we know for mapping the Iranian CML patients' treatment, we cannot lay on *abroad countries* results because of the underlying conditions diversity. Hence, we need to design studies to evaluate if there is any correlation between underlying situations of individuals (e.g. patients own characteristics, disease characteristics, drug regimens before imatinib resistance, etc.) in resistance occurrence and responses to imatinib. Moreover, we need to assess the priorities in the afterward treatment. The accuracy and validity of the available data are doubtful due to their study designs. Our results mostly are qualitative, not investigative and analytical; as a result, we need further evaluation of drug modifications outcomes by conducting appropriate clinical trials with

different arms (e.g. different accelerated dose and switching to other TKI).

Conflicts OF Interest

The authors indicated no potential conflicts of interest.

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