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Original Article

The potential gastrointestinal side effects of excipients in imatinib preparations

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Abstract

Aim: Chronic myeloid leukemia (CML) is a BCR-ABL positive myeloproliferative disorder characterized by clonal proliferation of the hematopoietic stem cells. Imatinib mesylate represents the most important agent associated with improved survival in CML that has been introduced for clinical use in 2000s. The original imatinib preparation Glivec ® was subsequently followed by the introduction of biosimilar products containing a variety of excipients. Gastrointestinal side effects represent the major limitation for therapeutic use of imatinib. This study was planned to examine whether excipients in the original and biosimilar imatinib products had any role in the emergence of GIS side effects.

Materials and methods: Excipients in imatinib preparations used for the treatment of chronic phase (CP) CML patients followed up and treated at the hematology department of Mersin University between 2000 and 2019 were analyzed with respect to their potential GIS side effects.

Results: Totally 42 CML patients included in the study. The median age was 53.2, and female:male ratio was 20:22. They had similar demographic characteristics as compared to previously reported CML populations. No patients had GIS side effect requiring drug discontinuation or switch to another agent. While bovine gelatin and polyvinyl alcohol had no significant effects on GIS side effects, those that contained titanium were found to be associated with a significant increase in the risk of GIS side effects (52%, contained titanium vs 0/2, contained no titanium). These side effects are less frequently in products that have lowest number of excipient types.

Conclusion: GIS side effects can be triggered by various excipients in imatinib preparations

Keywords: Chronic myeloid neoplasm; excipients; gastrointestinal side effects; imatinib; myeloproliferative neoplasm

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder with an annual incidence of 1.5/100.000 that is characterized by the clonal proliferation of the hematopoietic stem cells and that has an increasing incidence with age. This clonal proliferation is due to tyrosine kinase hyperactivity caused by the BCR-ABL fusion gene resulting from a translocation at t (9:22).

Until 2000s, CML was a largely mortal disease. However, after FDA approval was given to the tyrosine kinase inhibitor imatinib mesylate for the first time 2001, a new era has started in CML treatment, with general survival rates in CML patients approaching nearly to that of the normal healthy population (1). The original imatinib mesylate molecule, i.e. Glivec ®, was introduced by Novartis, with subsequent introduction of many other products. Currently, products in the Turkish market include Glitinib ® (Nobel), Imatis ® (Deva), Imatenil ® (Neutec), Imavec ® (Koçak), Glivon ® (Nobel), Imagliv ® (Saba), Maxinib ® (Centurion), and Pantikor ® (World).

Although all imatinib preparations may be associated with a wide range of side effects on many organ systems (cardiovascular, central nervous, musculo-skeletal, hematologic, renal, and respiratory systems), gastrointestinal side effects represent one of the major limiting factor in terms of the patient compliance to treatment (2).

Major GIS side effects include vomiting, nausea, diarrhea, abdominal pain, anorexia, abdominal distension, constipation, epigastric pain, and dyspeptic complaints. The frequency and severity of these complaints vary according to comorbid conditions and also according to the imatinib preparation utilized.

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Previous studies involved comparisons between the original molecule (Glivec) and other preparations (3), and between imatinib and 2nd generation tyrosine kinase inhibitors (dasatinib, nilotinib) (2) with respect to efficacy and side effect profile. However, to the best of our knowledge, no previous studies compared imatinib preparations between each other.

In this study, our aim was to examine the incidence of GIS side effects and their relationship with the excipients in chronic phase CML patients receiving different imatinib preparations.

MATERIALS and METHODS

A total of 48 chronic phase CML patients who were followed up and treated at the Hematology Department of Mersin University Hospital between 2000 and 2019 were enrolled in the study. Patients with CP-CML, BCR-ABL fusion gene negativity for a minimum duration of 1 year under imatinib therapy, between 18-80 age, had no other malignancies, were included. Patients with BCR-ABL fusion gene positivity, accelerating or blastic phase CML, treated without imatinib, younger than 18 and older than 80 years old, had another malignancy were excluded. Totally 42 patients were included in the study.

GIS side effects were classified using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5) criteria. Nausea, vomiting, diarrhea, abdominal pain, loss of appetite, dyspepsia, abdominal distension –bloating, constipation, oral ulceration, epigastric pain, GIS bleeding, gastritis, gastro-esophageal reflux, lipase elevated, ulceration, intestinal obstruction, intestinal perforation were the side effects that examined. Grading of them was made according to the severity of symptoms (mild to severe) that described in CTCAE v5.

Several drug groups have been defined and compared with respect to frequency and severity of side effects on the basis of the characteristics of the excipients as follows: those with (Imatenil and Imavec) or without (Glivec and Imatis) bovine gelatin; with (all preparations other than Glivec) or without (Glivec) titanium; with (Imatenil and Imatis) or without (Glivec and Imavec) polyvinyl alcohol; with few (Imatenil) or many (all preparations other than Imatenil) ingredients.

Statistical analysis

Datas in categorical structure are evaluated with numbers and percentages. Datas in continuous structure are evoluated with minimum-maximum mean and standart deviation values. Ki-square test is used to evoluate the relationship between variables with categorical structure. Z test is used in comparison of 2 ratios. Bar grafic is used in visual presentation of relationship between variables.

RESULTS

The median age of patients was 53.2 (35-74) years, with a median diagnosis age of 47.3 years (26-71) , female to male ratio of 20:22, and median follow up duration of 71.9 months (Range:4-197). (Table 1) The proportion of patients with at least one GIS side effect was 47.6% and 52.4% among male and female subjects, respectively.

Table 1. Demographic features patiens and ingredients of drugs

Characteristics	N	%
Gender (n, %)		
Female	20	48
Male	22	52
Median age	53.2	
Median age at diagnosis	47.3	Range:26-71
Median duration of follow-up (months)	42	Range:4-197
First preparation used		
Glivec	14	33.3
Imatis	21	50
Imavec	3	7.1
Imatenil	2	4.8
Glivon	2	4.8
Preparation currently used		
Glivec	2	4
Imatis	30	71
Imavec	2	4
Imatenil	8	19
No. of patients utilizing non-imatinib drugs due to comorbid conditions	11	26
Preparations with bovine gelatin	Imatenil Imavec	
Preparations containing polyvinyl alcohol	Imatenil Imavec	
Preparations without titanium	Glivec	
Preparations with fewest number of ingredients	Imatenil	

The initial treatment consisted of Imatis in half of the patients. A switch to another preparation was made in a total of 19 patients (45.2%) during the course of treatment. None of these treatment changes were due to side effects, but they were mainly due to cost issues, or less frequently due to difficulties associated with drug supply. Glivec was the most frequently discontinued agent, while Imatis (12 patients) was the most frequent second-line treatment, followed by Imatenil (6 patients). Eleven patients (26%) received additional treatment due to comorbid conditions.

In all patients, 50% of the them had at least one GIS side effects. Although statistically insignificant, Imatis (n=15, 50%), and followed by Imatenil (n=3, 62.5%) were associated with a higher incidence of side effects.

The most severe side effect was grade 2 gastritis (n=6), while the most frequent side effect was nausea (n=11), and all of them were grade 1. While there were no significant differences between different preparations with regard to nausea (p=0.22), this side effect occurred in 6 (20%), 4 (50%), and 1 (50%) patients receiving Imatis, Imatenil, and Imavec, respectively, with no nausea in 2 patients receiving Glivec.

Table 2. Frequency of side effects of dugs

		Glivec	Imatis	Imavec	Imatenil	p
		n (%)	n (%)	n (%)	n (%)	
No. of patients		2	30	2	8	
Side effects	no	2 (100)	15 (50)	1 (50)	3 (37.5)	0.351
	yes	0 (0)	15 (50)	1 (50)	5 (62.5)	
Nausea	no	2 (100)	24 (80)	1 (50)	4 (50)	0.220
	yes	0 (0)	6 (20)	1 (50)	4 (50)	
Vomiting	no	2 (100)	28 (93.3)	2 (100)	6 (75)	0.436
	yes	0 (0)	2 (6.7)	0 (0)	2 (25)	
Diarrhea	no	2 (100)	27 (90)	2 (100)	8 (100)	0.550
	yes	0 (0)	3 (10)	0 (0)	0 (0)	
Abdominal pain	no	2 (100)	27 (90)	2 (100)	7 (87.5)	0.829
	yes	0 (0)	3 (10)	0 (0)	1 (12.5)	
Loss of appetite	no	2 (100)	28 (93.3)	2 (100)	4 (57.1)	0.105
	yes	0 (0)	2 (6.7)	0 (0)	3 (42.9)	
Dyspepsia	no	2 (100)	25 (83.3)	2 (100)	5 (62.5)	0.350
	yes	0 (0)	5 (16.7)	0 (0)	3 (37.5)	
Abdominal distension -bloating	no	2 (100)	26 (86.7)	2 (100)	7 (87.5)	0.784
	yes	0 (0)	4 (13.3)	0 (0)	1 (12.5)	
Constipation	no	2 (100)	28 (93.3)	2 (100)	7 (87.5)	0.828
	yes	0 (0)	2 (6.7)	0 (0)	1 (12.5)	
Oral ulceration	no	2 (100)	29 (96.7)	2 (100)	8 (100)	0.877
	yes	0 (0)	1 (3.3)	0 (0)	0 (0)	
Epigastric pain	no	2 (100)	24 (80)	2 (100)	7 (87.5)	0.616
	yes	0 (0)	6 (20)	0 (0)	1 (12.5)	
GIS bleeding	no	2 (100)	30 (100)	2 (100)	8 (100)	-
	yes	0 (0)	0 (0)	0 (0)	0 (0)	
Gastritis	no	2 (100)	26 (86.7)	2 (100)	6 (75)	0.595
	yes	0 (0)	4 (13.3)	0 (0)	2 (25)	
Gastro-esophageal reflux	no	2 (100)	22 (73.3)	2 (100)	6 (75)	0.510
	yes	0 (0)	8 (26.7)	0 (0)	2 (25)	
Lipase elevated	no	2 (100)	30 (100)	2 (100)	8 (100)	-
	yes	0 (0)	0 (0)	0 (0)	0 (0)	
Ulceration	no	2 (100)	30 (100)	2 (100)	8 (100)	-
	yes	0 (0)	0 (0)	0 (0)	0 (0)	
Intestinal obstruction	no	2 (100)	30 (100)	2 (100)	8 (100)	-
	yes	0 (0)	0 (0)	0 (0)	0 (0)	
Intestinal perforation	no	2 (100)	30 (100)	2 (100)	8 (100)	-
	yes	0 (0)	0 (0)	0 (0)	0 (0)	

The second most frequent side effect was gastro-esophageal reflux, again with no significant association with preparations (p=0.51) (Table 2).

Vomiting, diarrhea, abdominal pain, reduced appetite, dyspepsia, abdominal distension, gastritis, constipation, oral ulceration, epigastric pain, and gastro-esophageal reflux occurred in at least 1 patient, while no patients had gastrointestinal bleeding, elevated lipase, peptic ulceration, intestinal obstruction, or perforation (Figure 1).

Patient survival was also did not differ significantly according to the preparation used for treatment.

When side effects were grouped according to the excipients, no significant differences between preparations with (Imatenil and Imavec, n=32) or without bovine gelatin (Glivec and Imatis, n=10) were found (46.9%, n=15 vs. 60%, n=6). When Glivec without titanium was compared with titanium containing preparations, no side effects were observed in 2 patients receiving Glivec treatment,

while at least 1 side effect was observed in 52% of those receiving treatment with titanium-containing preparations (n=21). Also, those with (Imatis and Imatenil, n=38) and without polyvinyl alcohol (Glivec and Imavec, n=4) were compared with respect to the proportion of patients with at least 1 side effect, no significant differences were detected (52%, n=20 vs. 25% n=1). In 37.5% of 8 patients receiving treatment with the product with lowest number of ingredients, i.e. Imatenil, 1 GIS side effect was reported, versus 47.0% in the 34 patients receiving treatment with the remaining agents.

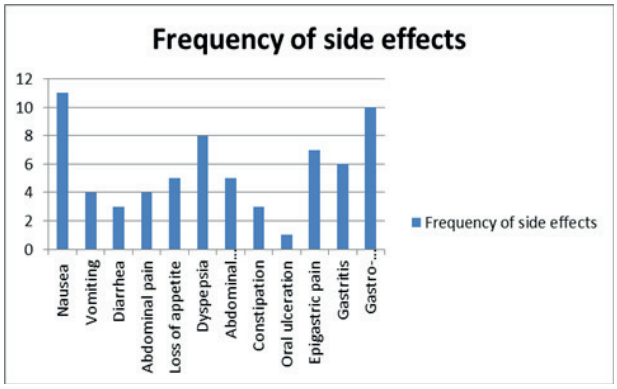

Figure 1. Frequency of side effects

DISCUSSION

Eleven years of follow up of the IRIS study showed that imatinib is associated with a considerable increase in survival in chronic phase CML patients, with no cumulative toxic effects over long-term use (1). Side effects occurring during treatment with an agent should be assessed and managed according to ECOG performance status, compliance to treatment, presence/absence of comorbid conditions and the associated treatments. In order to achieve standardization in the terminology used to describe side effects in cancer treatments, the National Cancer Institute Common Terminology Criteria Adverse Events (NCI-CTCAE) have been widely utilized (4). Similarly, we also used these criteria for our study purposes. A set of recommendations have been proposed by the European Leukemia Net (ELN) in order to assist management strategies based on the grade of side effects as defined by NCI-CTCAE(5). In a study from China, 35% of 548 patients were reported to have GIS side effects with Glivec (6). In our patient group, the most severe side effects included grade 2 events, and accordingly, treatment could be continued without discontinuation of imatinib in line with the ELN recommendations for patient management. Although Imatis was associated with a higher proportion of GIS side effects, this was not statistically significant (Figure 2). Again, similar to previous reports, nausea was the most common side effect in our patient (7) . Also, our patient group was similar to previously reported patient populations in terms of age and gender distribution(8) (Table 1).

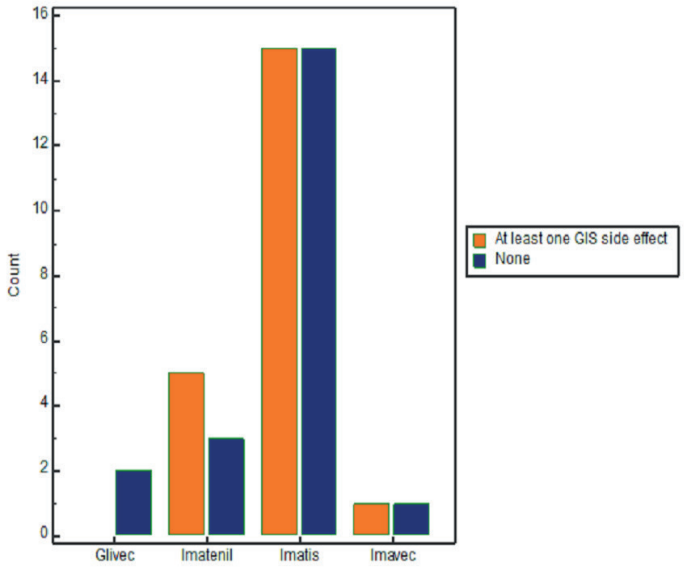

Figure 2. GIS side effects with different preparations

Nearly all medications contain excipients in addition to the main molecule responsible for the effect. Potential uses of excipients include filling (e.g., starch, saccharose), increasing gastric solubility, granule formation (e.g., glucose, gelatin, starch), facilitation of the ingestion (e.g. magnesium stearate), sweetening, increased water solubility, coating (e.g. methylcellulose), and packaging (PVC, aluminum) (9).

Such excipients should not only be functional, but also should have no negative impact on the efficacy and safety of the original molecule.

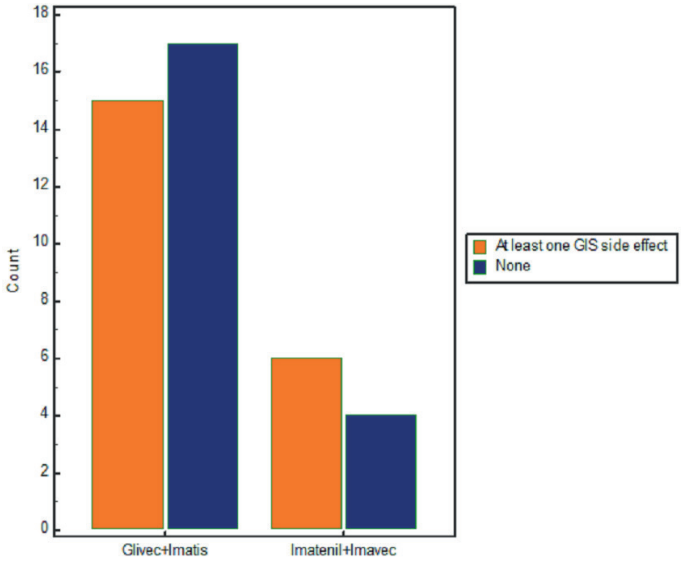

Figure 3. Association between bovine gelatin and GIS side effects

Of the imatinib preparations analyzed in this study, Imatenil and Imavec are presented in capsule form and contain bovine gelatin. Since no difference in side effect incidence was found according to the presence/absence of bovine gelatin, this excipient does not appear to have

any association with GIS side effect frequency (Figure 3). Of all preparations tested, only Glivec was free of titatium dioxide, and all side effects were observed in imatinib preparations that contain titanium as an excipient, which may suggests that titanium may be a triggering factor for GIS side effects. However, since only 2 patients received Glivec, larger studies are warranted to fully evaluate the role of titanium in the GIS side effect profile of these agents. Imatis and Imatenil, which contain polyvinyl alcohol in the packaging, were associated with an insignificant increase in the frequency of side effects, suggesting that this ingredient may be linked with side effects, although only further studies can reach a firmer conclusion (Figure 4). When the agent with fewer number of excipients, i.e. Imatenil, was compared with other agents containing higher number of excipients, an increase in the number of side effects was seen with increasing number of excipients, although this difference was insignificant.

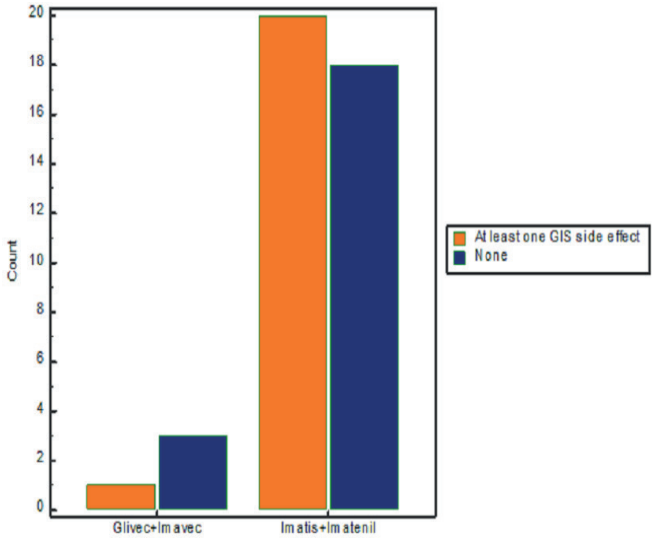

Figure 4. Association between polyvinyl alcohol and GIS side effects

Our major limitations were the paucity and the unproportional distribution of the number of patients, and ignoring the kinds of polypharmacy of comorbidities. It is beyond question that larger studies with demographically comparable patients (particularly with respect to comorbidities and use of poly-pharmacy) and similar number of patients in each specific medication group may shed much more light on the side effect profile of specific agents.

However, our study was at least the first of its kind in comparing GIS side effects according to excipients in imatinib preparations and may serve as a guidance for further studies.

In this study our aim was assess the GIS side effect profile of the excipients of imatinib preparations, and not of imatinib per se. For this purpose, first the excipients of each preparation was documented and the products were grouped and compared according to presence or absence of certain molecules. The side effect distribution across different brands was only presented as demographic data, clearly indicating the absence of any conflicts of interest.

CONCLUSION

GIS side effects can be triggered by various excipients in imatinib preparations. By determinig the GIS side effect potentials of the excipients, we can select the imatinib preparations more safely according to the patients' compliants.

Conflict of interest : The authors declare that they have no competing interest.

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Ethical approval: Mersin University ethics committee, 78017789/050.01.04/1289147.

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