CML HORIZONS

HYBRID MEETING 2024

Vilnius, Lithuania

24–26 May 2024

Drug interactions and Generic drugs

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Overview of presentation

- Drug interactions with TKIs
- Branded versus Generic TKIs
- Time for questions and discussion

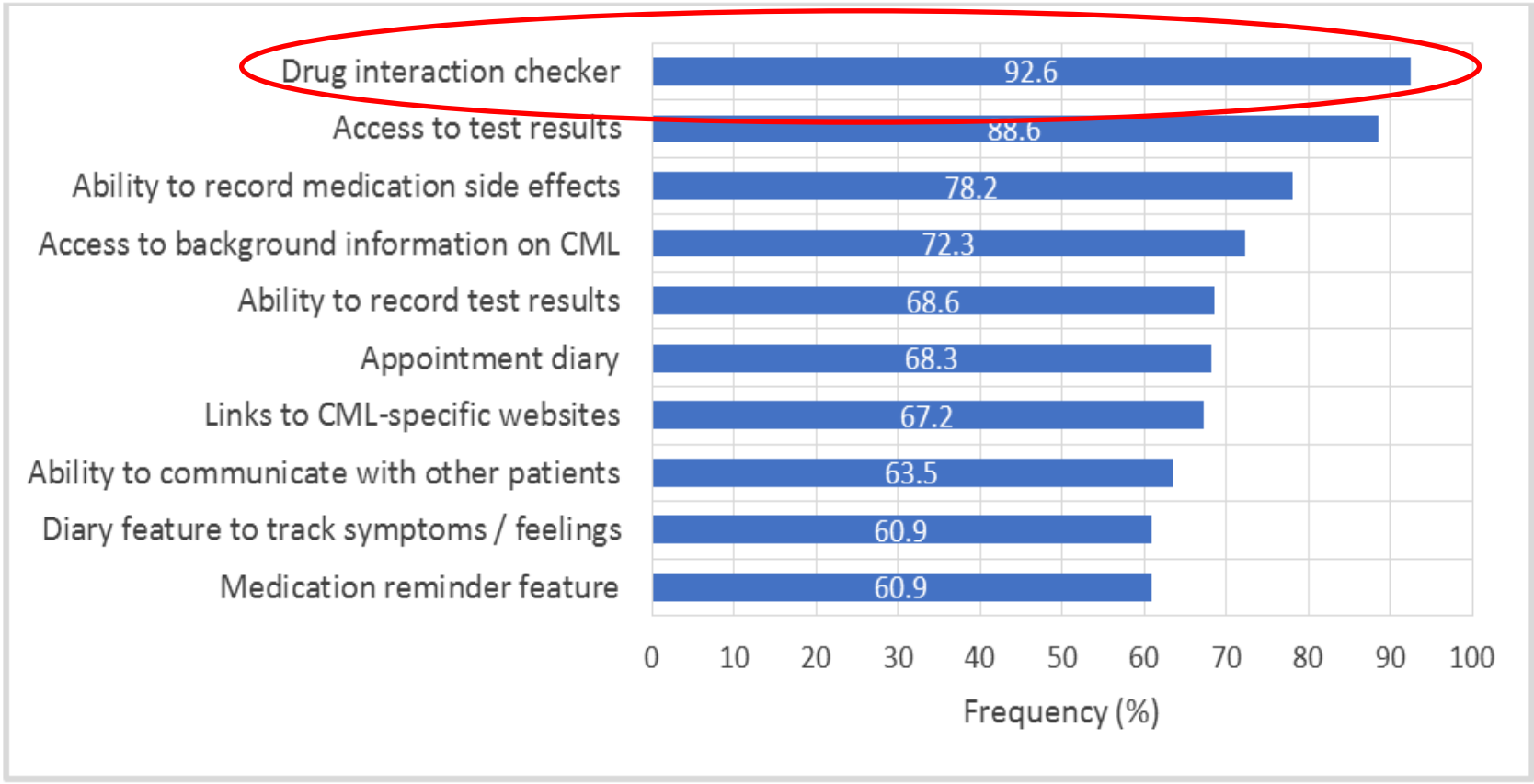
Drug interactions – definition and frequency

- A drug interaction occurs when the clinical effect of one drug is altered by the interference of another, although the interacting agent could also be a foodstuff, herbal product or environmental factor such as tobacco.

- Risk is associated with number of concomitant medicines:
  - If a patient is taking 2 drugs, risk is 6%
  - If a patient is taking 4 drugs, risk is 34%
  - If a patient is taking 6 drugs, risk is 72%

Drug interactions with TKIs – is this of interest to patients?

Figure 1: *Percentage of respondents stating they were "very interested" in app features [ranked according to popularity, n= 271]*



Khadam S, et al. An investigation of the use of app technology to support clinical management of patients with CML. Journal of Oncology Pharmacy Practice. 2023;29:1083.

Drug interactions with TKIs

- There are many different types of drug interactions in medicine

- In CML we are most interested in those interactions where one drug interferes with how the body handles another drug – these are known as pharmacokinetic interactions and can affect:
  - **Absorption**
  - Distribution
  - **Metabolism**
  - Excretion

Drug interactions with TKIs

- Pharmacokinetic interactions lead to an increase or a decrease in blood levels of the affected drug:

  ↑ levels = ↑ side effects

  ↓ levels = ↓ efficacy

- Works in both directions – TKIs for CML can be both the perpetrator and the victim of the interaction!

Drug interactions with TKIs - Absorption

- Many drugs need an acidic environment in the stomach to be optimally absorbed
- This may be a problem if a patient is on acid-suppressing medication e.g. a PPI such as lansoprazole or an H_2 antagonist such as famotidine.
- For example, the AUC (measure of exposure) for dasatinib in patients taking omeprazole shown to be reduced by 43%.

Drug interactions with TKIs - Absorption

- This interaction is important for:
  - Dasatinib
  - Bosutinib
  - Nilotinib??
    - Reduction in absorption but not clinically significant

- How to manage it
  - Avoid strong acid suppressants
  - Consider using an antacid (e.g. Gaviscon) at a different time of day to the TKI
  - Dasatinib anhydrous (Daruph) – does not need acid environment
  - Take the TKI with a glass of cola!

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Commentary

Pepsi® or Coke®? Influence of acid on dasatinib absorption

Randall W Knoebel[1] and Richard A Larson[2]

Abstract

Dasatinib is a second generation ABL kinase inhibitor used in the management of chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Dasatinib's bioavailability is highly dependent on gastric pH. When proton-pump inhibitors (PPIs) are co-administered with dasatinib, absorption is significantly reduced. Cola intake at the time of drug administration has been demonstrated to lead to relevant increases in the bioavailability for other acid labile drugs during PPI treatment. This manuscript reviews the relevant literature supporting a strategy of temporarily lowering the gastric pH with a carbonated beverage at the time of drug administration. The use of cola provides an easy to implement way to significantly improve dasatinib bioavailability, especially during concomitant use of a PPI.

Drug interactions with TKIs - Absorption

- What about the effect of food?

Drug	Instructions re food	Explanation
Asciminib	Take on empty stomach	To improve absorption
Nilotinib	Take on empty stomach	To reduce risk of QT prolongation (food increases absorption so risk of toxicities)
Bosutinib	Take with/after food	To improve absorption
Imatinib	Take with/after food	To reduce GI side effects e.g. nausea
Dasatinib	Take anytime	
Ponatinib	Take anytime	

Drug interactions with TKIs - metabolism

- There are a family of enzymes in the liver responsible for breaking down drugs (and also toxins and nutrients)

- Called Cytochrome P450 family. Over 50 subtypes:
  - 6 subtypes responsible for >90% of hepatic drug metabolism
  - 1 subtype (**CYP3A4**) responsible for >50%

Drug interactions with TKIs - metabolism

Substrate	CYP3A4 inhibitor	CYP3A4 inducer
Bosutinib	Asciminib (weak)	
Dasatinib	Dasatinib	
Imatinib	Imatinib	
Nilotinib	Nilotinib	
Ponatinib		
Asciminib ??		
Simvastatin	Clarithromycin	Phenytoin
Ciclosporin	Voriconazole	Rifampicin
	Grapefruit juice	St John's Wort

Drug interactions with TKIs - metabolism

- TKIs can also affect other enzymes involved in metabolism and drug transport……
  - Imatinib and asciminib inhibit CYP2C9 so could increase warfarin levels
  - Ponatinib and asciminib inhibit the transporter protein PGP so could increase digoxin levels

Drug interactions with TKIs – additive toxicities

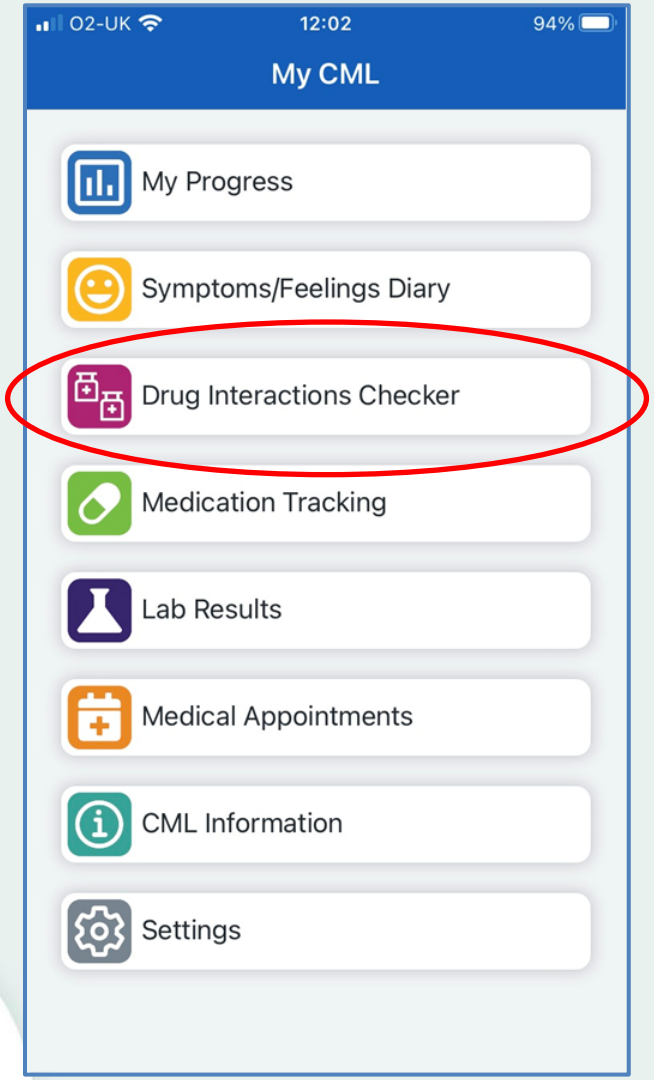
- We should also be aware of pharmacodynamic interactions (this relates to what the drug does to the body i.e. clinical effects or side effects)
- Main issue to be aware of is QT interval prolongation which increases the risk of heart rhythm abnormalities
  - Applies to asciminb, bosutinib, dasatinib and nilotinib
  - Watch out for other drugs that could prolong QT interval e.g. clarithromycin, chloroquine, moxifloxacin

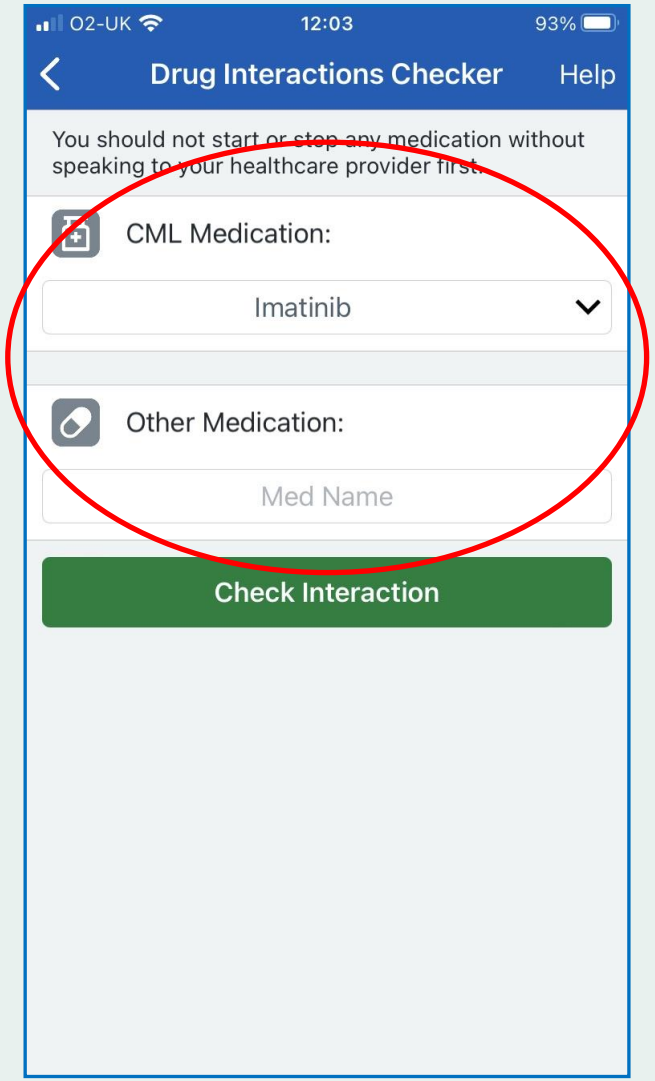
Where to find info on drug interactions

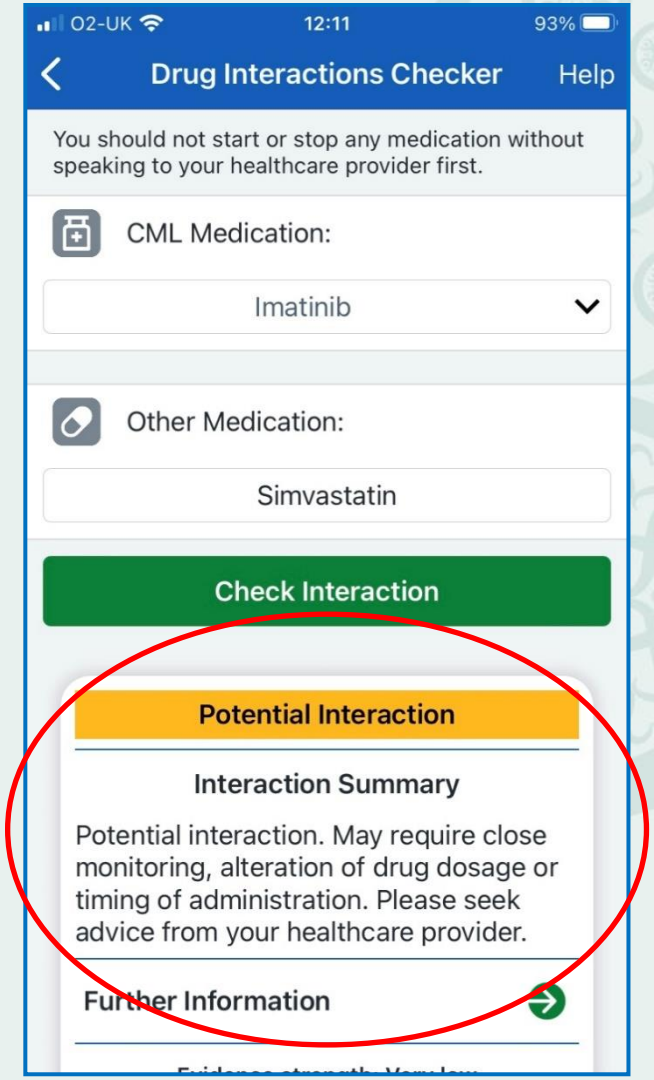
Table 2. Useful websites on drug interactions

Website	Details
www.medicines.org.uk	Summaries of product characteristics for medicines licensed in the UK
www.drugs.com	Contains a comprehensive drug interaction checker
http://medicine.iupui.edu/clinpharm/ddis/	Cytochrome P450 system drug interactions table
www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs	Memorial Sloan Kettering Cancer Center site with information on herbal and other complementary therapies

Drug interactions feature in MyCML app







Further reading

- Duncan N. Pharmacokinetic drug interactions in haematology. *Myeloid and Lymphoid disorders in practice* 2016; 1: 15-17

- Fang Cheng, Hongxiang Wang, Weiming Li, Yu Zhang. Clinical pharmacokinetics and drug–drug interactions of tyrosine-kinase inhibitors in chronic myeloid leukemia: A clinical perspective. *Critical Reviews in Oncology/Hematology* 2024; Volume 195, March.

Branded vs. Generic drugs (1)

- When a drug is first approved, the company who make it has market exclusivity for 20 years.
- Once it goes “off patent”, other companies are allowed to market their own versions - generics
- Longstanding debate about merits of branded versus generic drugs
  - If you have a headache do you insist on Nurofen® or would you take ibuprofen?

Branded vs. Generic drugs (2)

- Is there any difference between them?
  - Not in terms of the active ingredient
  - But may be differences in terms of excipients i.e. bulking agents, colourants, preservatives etc.
  - May differ in size, shape, taste

6.1 List of excipients

Tablet core:

Cellulose microcrystalline

Crospovidone (type A)

Hypromellose

Magnesium stearate

Silica, colloidal anhydrous

Tablet coat:

Iron oxide, red (E172)

Iron oxide, yellow (E172)

Macrogol 4000

Talc

Hypromellose

Different excipients……..

	Tablet core:								Tablet coat:									
	Microcrystalline cellulose (E460)	Crospovidone / Crospovidone (Type A) E1201	Hypromellose	Magnesium stearate (E572)	Silica, colloidal anhydrous	Povidone (E1201)	Calcium hydrogen phosphate	Low substituted hydroxypropyl cellulose E463	Hypromellose / Hydroxypropylmethyl cellulose	Talc	Iron oxide yellow (E172)	Macrogol	Macrogol 400	Iron oxide red (E172)	Titanium dioxide (E171)	Poly(vinyl alcohol)	Macrogol 4000	Polyethylene glycol
Glivec film-coated tablets: Novartis	X	X	X	X	X				X	X	X	X		X				
Imatinib film-coated tablets: Accord	X	X	X	X	X				X	X	X			X				X
Imatinib film-coated tablets: Amarox				X					X	X		X			X			
Imatinib film-coated Tablets: Dr. Reddy's				X					X	X		X			X			
Imatinib film-coated tablets: Sandoz	X	X	X	X	X				X	X	X			X			X	
Imatinib film-coated tablets: Teva		X		X			X			X	X	X		X	X	X		
Imatinib film-coat tablets: Zentiva	X	X		X	X	X		X	X	X	X		X	X				

Source for table: https://www.sps.nhs.uk/articles/switching-between-imatinib-preparations/

Bioequivalence

- Generic products have to work the same way in the body before they are approved:

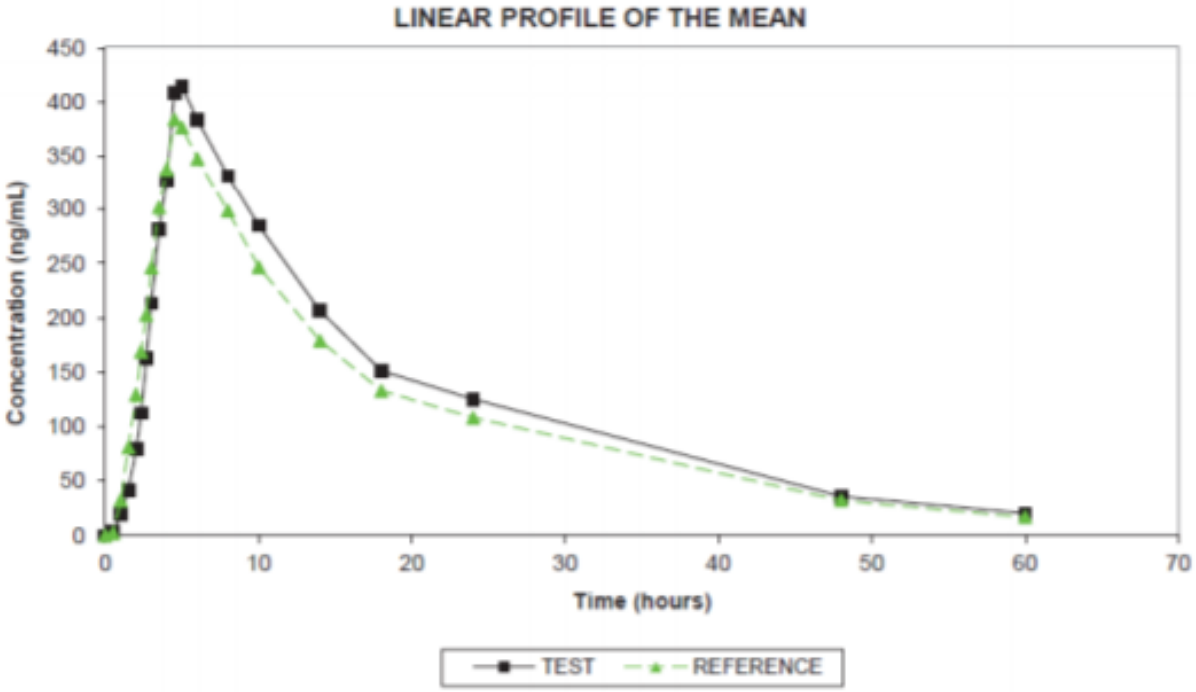


Figure 1: Linear profile of the mean imatinib plasma concentration versus time (n=24).

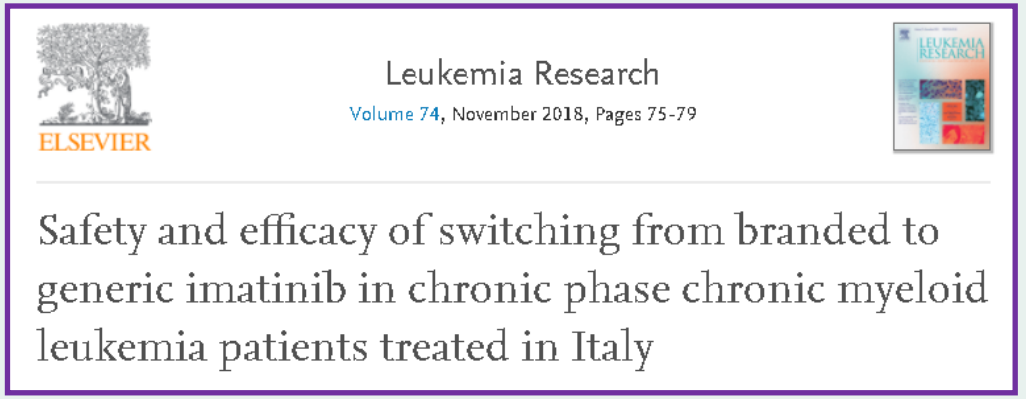
Price considerations

- When a drug comes off patent, the price charged by generic manufacturers is expected to be significantly lower:

- Glivec® (Novartis) – was approx. $3,000/month

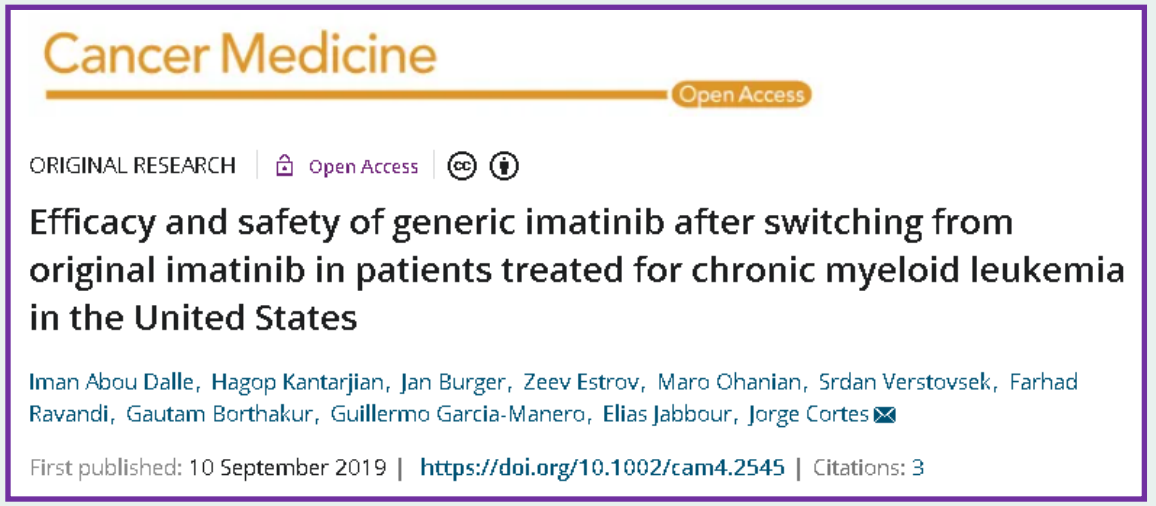
- Imatinib (Generic) - **$35/month**

Efficacy and tolerability (1)



- 294 patients
- New or worsening side effects in 17%
- 3% switched back to branded or to alternative TKI
- Savings of 3 million euros

Efficacy and tolerability (2)



Cancer Medicine

Open Access

ORIGINAL RESEARCH | Open Access

Efficacy and safety of generic imatinib after switching from original imatinib in patients treated for chronic myeloid leukemia in the United States

Iman Abou Dalle, Hagop Kantarjian, Jan Burger, Zeev Estrov, Maro Ohanian, Srdan Verstovsek, Farhad Ravandi, Gautam Borthakur, Guillermo Garcia-Manero, Elias Jabbour, Jorge Cortes

First published: 10 September 2019 | https://doi.org/10.1002/cam4.2545 | Citations: 3

- 38 patients
- 39% patients reported new or worsening adverse events, including 5 (13%) with oedema, 8 (21%) muscle cramps, 7 (18%) nausea, 6 (16%) diarrhoea, and 5 (13%) fatigue.
- No evidence of loss of efficacy

Why are there more side effects?

- Probably related to differences in excipients
- About 10-15% of our imatinib patients have had issues with one or more generic. A few have switched back to Glivec.
- If you are unhappy with side effects associated with your generic speak to your consultant.
  - We have some patients on Sandoz brand as identical to Novartis product

Current and future state of generic market

- Dasatinib came off patent 2022/2023
- Nilotinib and Bosutinib should come off patent in 2024
- Generic nilotinib already available in >40 LMICs via special licensing agreement from Oct 22

Country List

Bangladesh, Belize, Benin, Bhutan, Bolivia (Plurinational State of), Burundi, Cambodia, Cameroon, Congo, democratic Republic of the, Ethiopia, Ghana, Guinea, Haiti, Honduras, Kenya, Kosovo, Lao People's Democratic Republic (the), Madagascar, Malawi, Mongolia, Mozambique, Nepal, Nicaragua, Papua New Guinea, Rwanda, Senegal, Tanzania, United Republic of, Togo, Uganda, Zambia, Angola, Côte d'Ivoire, Egypt, El Salvador, Georgia, Guatemala, Indonesia, Morocco, Pakistan, Philippines, Sri Lanka, Tajikistan, Tunisia, Uzbekistan

Ensuring the patient voice is heard (1)

- Clinical staff may assume that switch to generic is always safe and effective
  - Effective – YES
  - Safe – tolerability concerns??

- Questions to consider…
  - Are patients being told about the switch to generic?
  - Are they involved in the decision-making process?
  - What side effects are being reported?
  - Do patients have the opportunity to switch back?

Ensuring the patient voice is heard (2)

- Currently working on proposal for questionnaire survey of CML patients on their experiences with generic TKIs

- Topics to explore……?
  - Communication by HCPs
  - Engagement with patients
  - Patient concerns
  - Experience of side effects
  - Impact on QoL

- Previous surveys have been facilitated by CML Support and CML Facebook UK. Would be great to have CML Advocates Network on board also.

- Thank you for your attention
- Time for questions and discussion…….