Comparison of Efficacy and Safety of Imatinib and Dasatinib in the Treatment of Chronic-phase Chronic Myeloid Leukemia

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Abstract. Chronic-phase chronic myeloid leukemia (CML-CP) treatment has significantly improved in recent years. The generational development of small molecule tyrosine kinase inhibitors (TKIs) such as Imatinib and Dasatinib, has revolutionized the treatment of CML. Their mechanisms and efficacy have been clear, but there is no literature review to summarize or comprehensively compare their efficacy and safety. Studies have revealed that second-generation TKI therapy yields noticeably greater response rates than imatinib and there is no marked difference in treatment-related adverse events between the two therapies. According to this direction, A double-therapies analysis was performed to assess the efficacy and tolerability of various front-line treatments for individuals with CML-CP. Both direct and indirect comparisons between the various treatment choices were taken into account in this general analysis. The author took Imatinib and Dasatinib as the main comparison objects and provide a comprehensive assessment of the two available therapies for CML-CP. By comparing the efficacy outcomes and adverse effects (AEs), the study was aimed to identify the treatment options that are both highly effective and well-tolerated for patients in general.

Keywords: Chronic myeloid leukemia, chronic-phase, Imatinib, Dasatinib, CCyR.

1. Introduction

Chronic myeloid leukemia (CML) is a malignant myeloproliferative tumor occurring in hematopoietic stem cells. The American Cancer Society estimates that about 15% of all new cases of leukemia are CML and mortality of this kind of disease is up to 14.7% comparing with 6% (2016-2020) of all leukemia [1, 2]. Therefore, it's necessary to reinforce the medical research and development of CML.

The pathogenesis of CML is a genetic change in Philadelphia (Ph) chromosome T (9; 22). Specifically, the Abelson murine leukemia (ABL1) gene on chromosome 9 connect to the breakpoint cluster region (BCR) gene on chromosome 22, which led to the formation of BCR-ABL fusion gene [3]. This gene can encode hybrid protein which has abnormal tyrosine kinase (TK) activity through sequential downstream reactions involving RAS or RAF and thus leads to abnormal pathway activation, which finally results in abnormal leukemogenesis causing malignant proliferation without apoptotic signals as well as apoptosis of hematopoietic stem cells [4, 5]. CML usually progresses slowly and can be divided into three phases: chronic phase (CML-CP), accelerated phase (CML-AP) and blast phase (CML-BP). Patients are usually diagnosed in CP, so the subjects of this study are all CML-CP patients [6].

Before 2000, general chemical medicines have been the only available medication therapies for CML. Chemical drugs include busulfan, hydroxyurea and interferon-alfa (IFN-a) which presented modest curative effect, side effects as well as toxicity, leading to a poor prognosis that expected survival of four to 6 years [7]. Yet thanks to the development of the small molecule tyrosine kinase inhibitors (TKIs) in the last 2 decades, there has been a breakthrough in CML treatment methods. TKI, as a targeted drug, can effectively interfere with BCR-ABL1 oncoprotein and adenosine triphosphate (ATP) to prevent the proliferation of malignant cloned cells.

The first generation TKIs, known as Gleevec or Imatinib Mesylate, marks the beginning of TKI research and development. It has been analyzed that the average survival time of patients with Imatinib therapy is about 20 years compared with the previous 6 years. 10 years ago, second generation TKIs such as Dasatinib have been developed as feasible alternatives [8]. Dasatinib can be

taken orally and has 350 times the potency of imatinib in vitro [6]. In recent years, TKI resistence among CML patients is increasing, and more than half of them have mutations in BCR-ABL kinase region, among which T3151 mutation is detected. Therefore, a drug for TKI resistance or intolerance - Ponatinib has been approved in the world, which is also known as the third generation of TKIs. The literature review involves both Imatinib and Dasatinib, rather than the third-generation drugs. In this review, the efficacy of Imatinib and Dasatinib will be presented by showing intuitive data.

On one hand, second generation TKIs show considerably stronger efficacy in the treating CML-CP. Dasatinib, in particular, exhibits about three times higher odds of complete cytogenetic response (CCyR) at 6 months compared to imatinib. Both dasatinib and nilotinib outperform imatinib in terms of CCyR at 12 months and 18 months [9]. Apart from the CCyR, dasatinib is also better than imatinib in several other efficacy indicators such as major molecular response (MMR), progression-free survival (PFS) and so on [10-12].

On the other hand, there is no marked difference on the incidence of treatment-related adverse events (AEs) between these two therapies, which may lead to headache, diarrhea, hypophosphatemia, dizziness, nausea, vomiting, muscle spasms et al. However, dasatinib may bring about greater toxicity. In DASCERN study, both dasatinib arm and imatinib exhibit similar non-hematologic and hematologic AEs but patients seemed to respond more strongly to dasatinib based on the incidence [9]. Moreover, in another multicenter study, several cooperating organizations discovered more AEs of Grade 3/4 (mainly hematologic) occurred in the Dasatinib treatment [13].

2. Methods

2.1. Data Source and Materials

A thorough review of the literature was conducted and relevant extracted data was utilized to carry out an overall analysis that involved indirectly comparing the outcomes of the two interventions (Imatinib and Dasatinib). The aim was to gather comprehensive and up-to-date information, so the data and literature of recent ten years were selected. The inclusion criteria considered the type of publication, treatment options, and the requirement to report information on the endpoints such as survival rates, CCyR, MMR and so on.

2.2. Description of Relevant Idicators

2.2.1. Efficacy indicators

Complete cytogenetic response (CCyR) is used to describe the absence of abnormal chromosomes or genetic mutations in the marrow. Event-free survival (EFS) assesses the time participants remain free from predefined events. Overall survival (OS) measures general survival regardless of cause of death. Progression-free survival (PFS) evaluates the time before disease progression occurs.

These 4 terms above are regarded as important endpoints in the trials which provide valuable information about the efficacy and impact of treatments in clinical trials and patient management. Deep molecular response (DMR; commonly MR4.5) and major molecular response (MMR) are both terms used in the context of treating CML. DMR indicates a significant reduction or elimination of cancer cells at the molecular level. It is typically defined as a reduction of at least 4-log (or 0.01% on the international scale) or more below a standardized baseline level of BCR-ABL1 transcripts, which are produced by the abnormal gene known as BCR-ABL1 that drives CML. In contrast, MMR refers to a less stringent measure of treatment response. It is defined as a reduction of at least 3-log (or 0.1% on the international scale) or more below the same standardized baseline level of BCR-ABL1 transcripts.

2.2.2. Security indicators

The Charlson Comorbidity Index (CCI) was used to calculate the comorbidity burden for each patient at the time of diagnosis. The effectiveness and safety data were then divided into 7 different

groups according to different CCI score categories. Higher scores indicate heavier load of comorbidities.

Treatment-related adverse events (AEs) occurred during medication are also essential indicators. The incidence of each AE such as Headache, Diarrhea, Hypophosphatemia and Pleural Effusion are included.

2.3. Analyzing Methods

The data mainly comes from two kinds of trials: DASCERN (NCT01593254) trial conducted to investigate the underlying advantages of early transitioning to dasatinib in patients who did not achieve a favorable early molecular response (EMR) to first-line imatinib [11]. There are 3 levels of endpoints in total (Figure 1) [11].

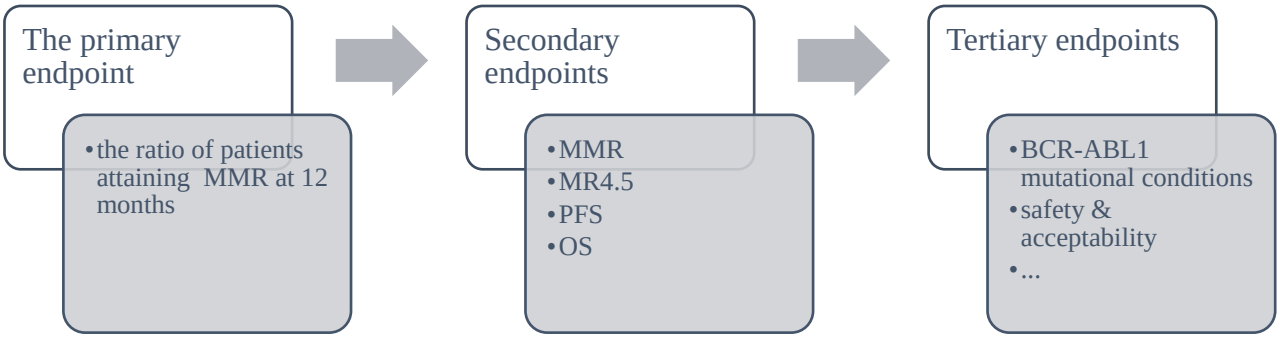


Figure 1. The endpoints of DASCERN

DASISION was a phase 3 clinical trial (NCT00481247) conducted internationally, involving CML-CP patients and it was also aimed to compare the efficacy of the same two drugs. In the trial, patients were randomized to take either 100 mg dasatinib or 400 mg imatinib once daily. Patients' CCI was calculated at diagnosis. Rates of achieving MMR and MR4.5 and time evaluation were compared between treatment groups [14].

3. Results and Discussion

In all the trials and analysis, achieving CCyR and MMR were considered the primary comparison factors, with safety and tolerability as secondary factors. Therefore, this review will mainly summarize and compare the data reflecting the efficacy of the drug, and there will also be a section of the safety comparison.

3.1. Efficacy

3.1.1. A Systematic evaluation of Efficacy

Data from a total of 3 clinical studies were included in the analysis and were deemed to be of statistical and clinical significance (Table 1) [9, 11].

In the facet of CCyR, the data of dasatinib all exceeds that of imatinib (Figure 2 and 3, CrI: credible interval. “Imatinib 400 daily”: reference category) [9]. A rough judgment can be made that particularly at 6 months, CCyR of dasatinib was almost three times greater than imatinib. In both six-month and twelve-month evaluations, the reported probabilities of achieving a CCyR were higher than imatinib in the DASISION study compared to all other trials that were observed [9].

Table 1. The included studies

Study	Study characteristics					
	Background	Study period (months)	Drug Administration (SID)	Number of patients	Median follow up (months)	% lost to follow up (months)
DASISION	Multicentre, Randomised, Phase lll		Dasatinib 100 mg	259	18	15%
			lmatinib 400 mg	260		19%
S0325 Intergroup	Open Label, Randomised, Phase ll	12	lmatinib 400 mg	127		
			Dasatinib 400 mg	126		
DASCERN	Multicentre, Randomised, Phase 2b	12	Imatinib 400 mg	86	24	
			Dasatinib 400mg	174		

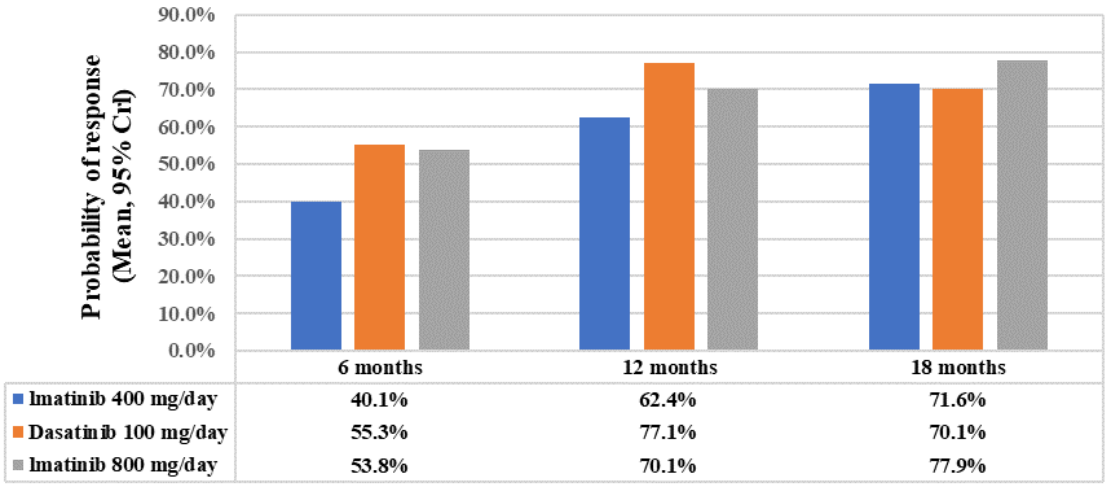


Figure 2. CCyR difference (CCyR indicator 1)

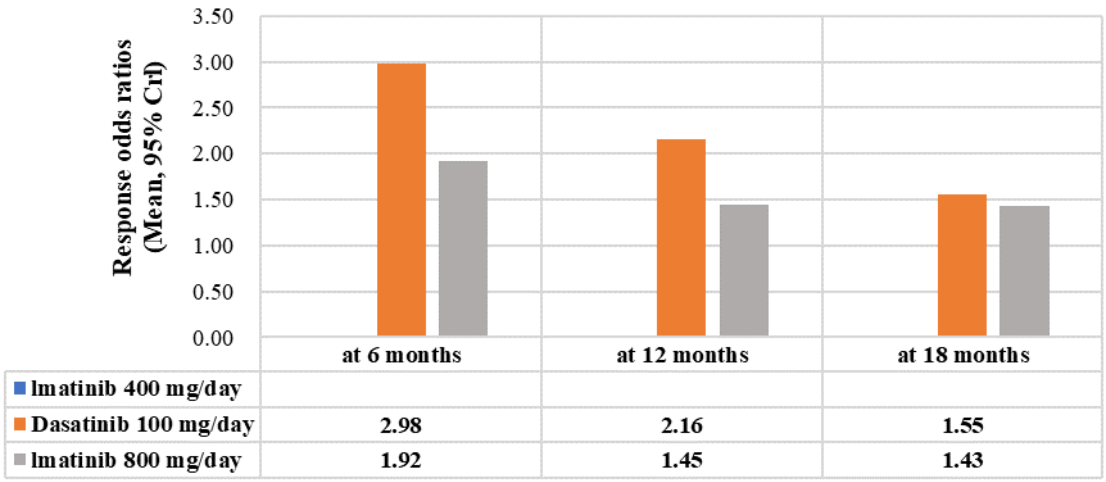


Figure 3. CCyR difference (CCyR indicator 2)

In the facet of MMR, the valid data for MMR is only recorded at 12 months (Figure 4 and 5) [9]. In particular, dasatinib had chances of response that were no less than two times compared to the equivalent of imatinib arm.

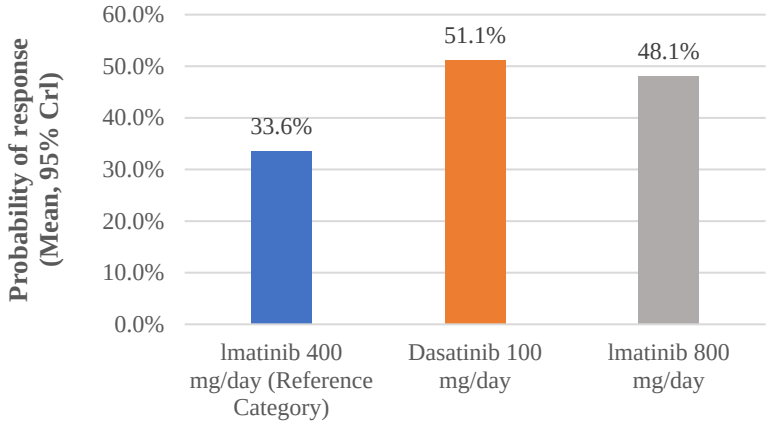


Figure 4. MMR difference at 12 months (CCyR indicator 1)

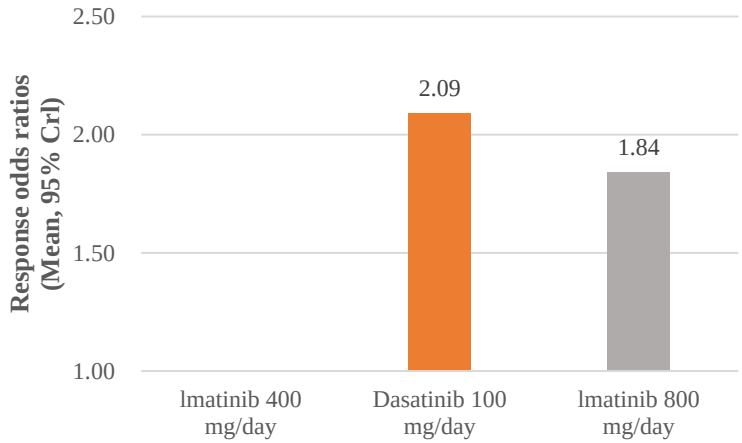


Figure 5. MMR difference at 12 months (CCyR indicator 2)

The findings obtained from the analysis align with the results reported in the original clinical studies. Specifically, the overall analysis confirms that dasatinib therapeutically preferable than imatinib in terms of achieving CCyR and MMR at various timing.

3.1.2. Comparison of efficacy based on DASCERN trials

In the DASCERN trial (Figure 6), during the last 5 years of tracking, it was noted that CML-CP patients who switched to dasatinib early after experiencing suboptimal responses to imatinib for 3 months achieved sustained clinical benefits [11]. Comparatively, the dasatinib rates of achieving MMR and DMR were consistently over imatinib (Figure 7).

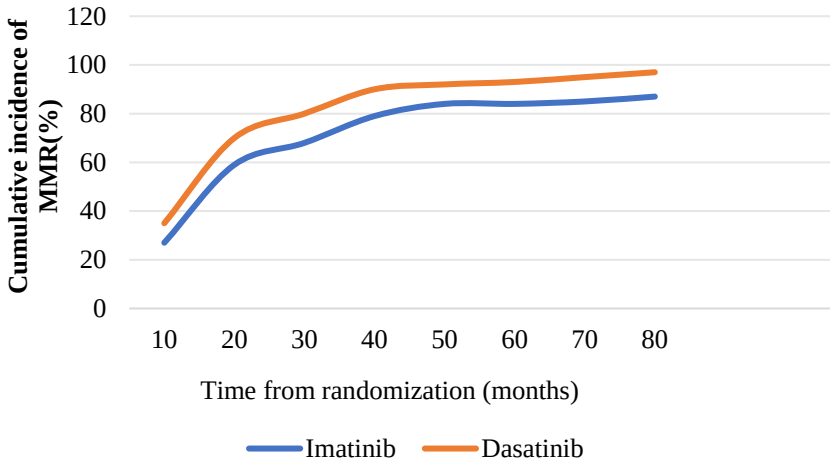


Figure 6. MMR rates by ITT population

Figure 6: Patients who achieved complete hematologic response but did not attain early molecular response (EMR) 3 months after starting imatinib 400mg were randomized in a 2:1 ratio to switch early to dasatinib (100mg) or continue with imatinib (≥400mg). If patients failed to achieve the desired outcomes with imatinib, they were allowed to cross over to dasatinib. The population intent to treat (ITT) comprised of all the patients who were allocated to either arm, regardless of whether or not they underwent crossover.

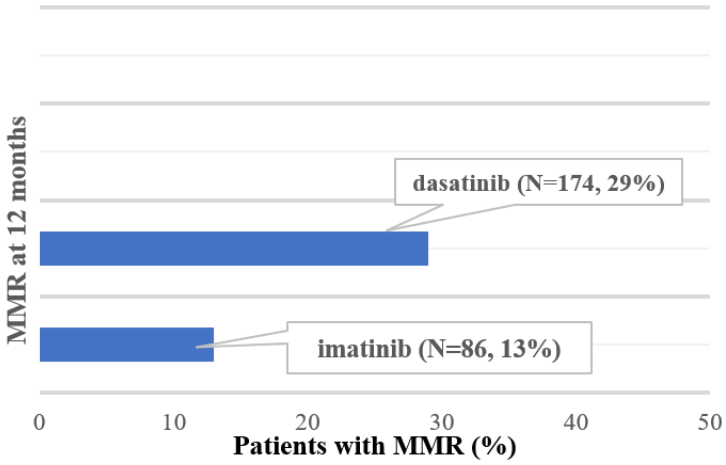


Figure 7. MMR after 12 months

Regarding the PFS and OS rate, datas from the ITT population in NACSERN proved that an early crossover to dasatinib from imatinib after the first generation TKI treatment failure could raise the surival rates at 24 months to some extent (Table 2).

Table 2. PFS, OS comparison

	randomized to dasatinib (%)	randomized to imatinib (%)	Switch Status		
			Early Crossover (%)	Late Crossover (%)	Imatinib without crossover (%)
PFS at 24 months (ITT population 1)	96	95	96	93	/
OS at 24 months (ITT population 2)	98	97	98	96	98

3.1.3. Comparison of efficacy based on DASISION trials

5-year tracking of DASISION study verified deeper and quicker molecular responses with dasatinib [13]. In total, 3% patients had Charlson Comorbidity Index (CCI) 2-4, 50% had CCI 5-6, and 47% had CCI ≥ 7 [13]. In conclusion, dasatinib showed a significantly higher MMR rate compared to imatinib in both MMR rates and MR4.5 rates (Table 3).

Table 3. MMR & MR4.5 difference

	Different grades of CCI among the patirents					
	CCI 2-4		CCI 5-6		CCI ≥ 7	
	Imatinib	Dasatinib	Imatinib	Dasatinib	Imatinib	Dasatinib
MMR (%)	57.1	85.7	64.8	81.1	64.0	70.8
MR4.5 (%)	14.3	71.4	29.7	42.4	39.2	45.0

Another salient superiority was that the average time for completing MMR was noticeably shortened with dasatinib instead of imatinib in the CCI ≥ 7 group (12.0 vs 21.4 months, Figure 8).

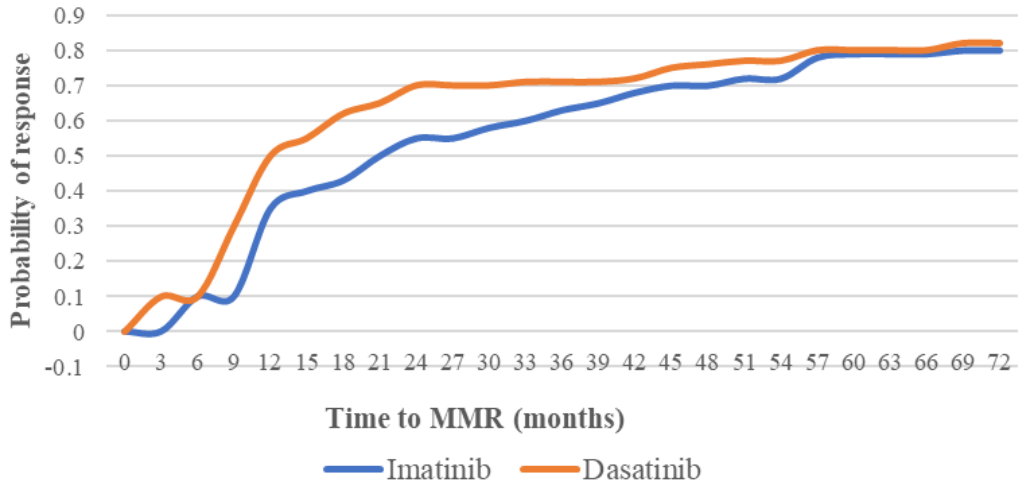


Figure 8. Time to MMR in patients with CCI≥7

3.2. Safety

In DASCERN study, the trial recorded all grades of adverse reactions and grade 3-4 adverse reactions for both drugs. In the dasatinib group, 82% of patients experienced treatment-related AEs, while in the imatinib group, the percentage was 78% [11]. The percentage corresponding to each specific AE is shown in Figure 9.

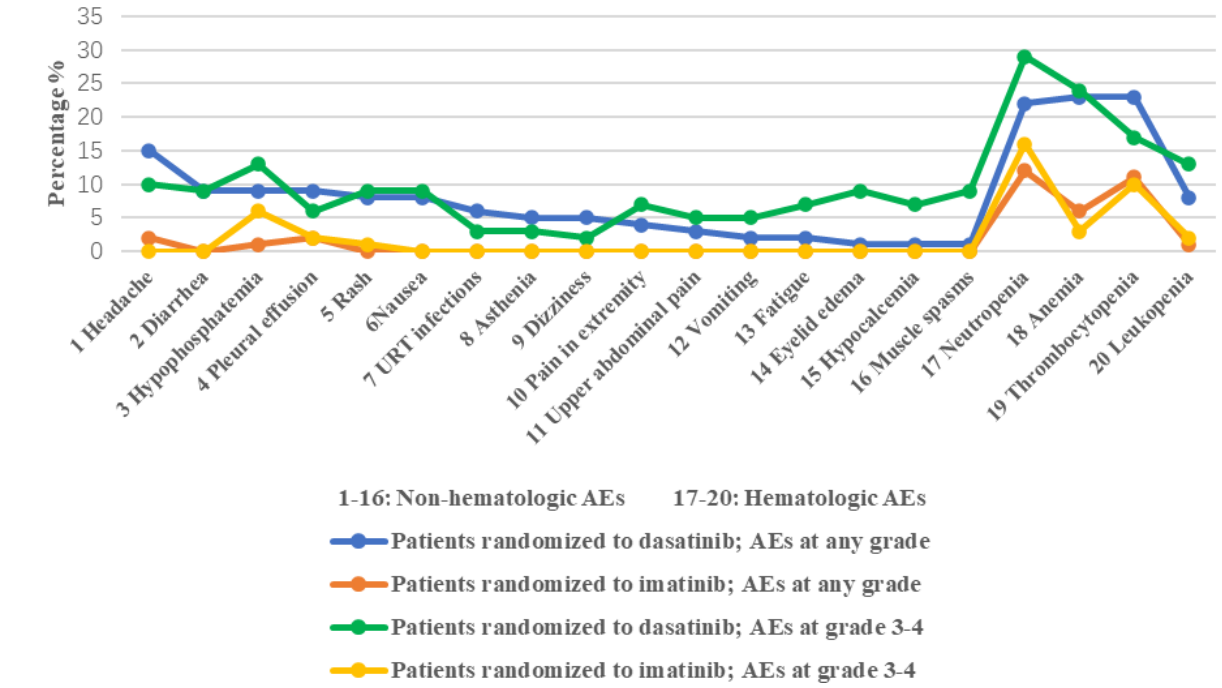


Figure 9. AEs to each drug alone

Figure 9 suggests that patients receiving imatinib as initial treatment have marginally higher drug tolerability and safety than those receiving 2nd TKI dasatinib. Imatinib alone seems to be better, but in reality, patients receiving first-generation drug treatment develop resistance or intolerance to imatinib in the early stages of the therapy, and these people have to switch to dasatinib.

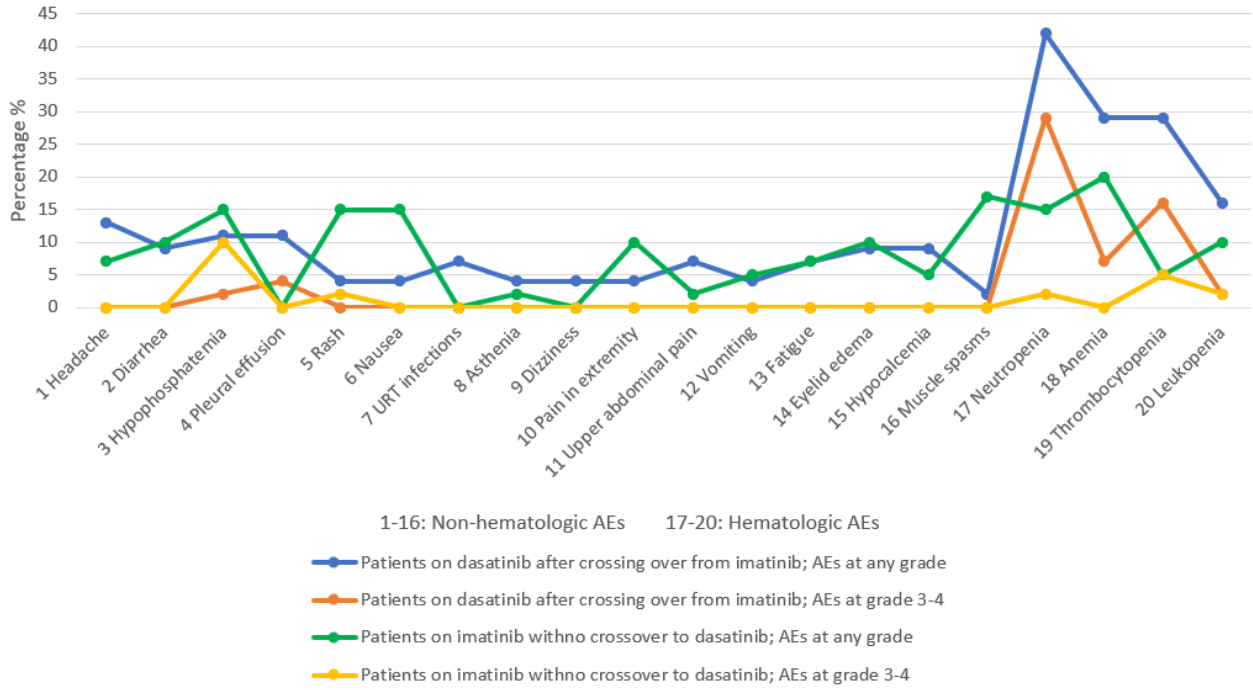


Figure 10. AEs to each drug alone

Figure 10 illustrates that the initial changeover to dasatinib in the DASCERN trial did not result in an upsurge in the proportion of AEs. Furthermore, those who transitioned to dasatinib and those who stayed on imatinib saw identical amounts of treatment-related hematologic side events.

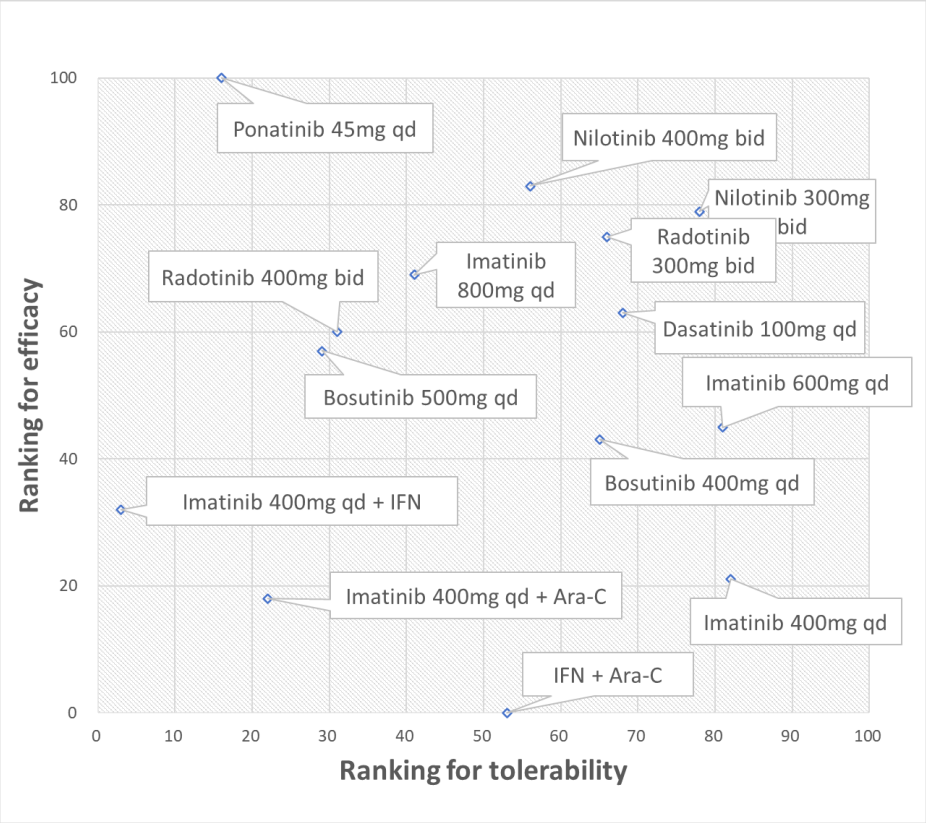


Figure 11. In a comprehensive comparison of generation of TKIs

In a comprehensive comparison of TKIs (Figure 11), idasatinib treatment (600mg QD) presents a superior efficacy and acceptability. Due to the low tolerability, high doses of imatinib (800 mg QD) are only recommended for patients in AP/ BP or those with suboptimal response in CML-CP [15].

4. Conclusion

In terms of efficacy, Dasatinib has shown better results than Imatinib in terms of CCyR and MMR. Patients treated with Dasatinib had significantly greater odds of achieving CCyR and MMR in comparison to those on Imatinib. Dasatinib therapy has also demonstrated improved overall survival and reduced likelihood of disease progression.

Regarding adverse events, there is no significant difference between the two types of TKIs. Both therapies can cause various treatment-related side effects such as headache, diarrhea, hypophosphatemia, dizziness, nausea, vomiting, and muscle spasms. However, it is worth noting that there were cases of pleural effusion associated with Dasatinib treatment, resulting in some patients discontinuing the drug due to toxicity. Additionally, hematologic toxicity was more frequently observed with Dasatinib compared to Imatinib.

Overall, the development of TKIs, particularly Imatinib and Dasatinib, has significantly improved the treatment outcomes for CML patients. These targeted therapies have led to higher response rates, prolonged survival, and reduced disease progression. However, further research is still needed to address TKI resistance and optimize treatment strategies for CML.

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