Research Article

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Journal of Health & Medical Economics
ISSN 2471-992

2025
Vol.11 No.1:102

Impact on Cost of Care of Concomitant Prescribing of Acid Reducing Agents with Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia Patients: A US Payer Perspective

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Received date: April 28, 2025, Manuscript No. IPJHME-25-20347; **Editor assigned date:** April 30, 2025, PreQC No. IPJHME-25-20347 (PQ); **Reviewed date:** May 14, 2025, QC No. IPJHME-25-20347; **Revised date:** May 21, 2025, Manuscript No. IPJHME-25-20347 (R); **Published date:** May 28, 2025, DOI: 10.36648/2471-9927.11.1.102

Citation: Kilcoyne A, Nathan R, Anderson C, Moore A, Russo P (2025) Impact on Cost of Care of Concomitant Prescribing of Acid Reducing Agents with Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia Patients: A US Payer Perspective. J Health Med Econ Vol.11 No.1:102.

Abstract

Context: Tyrosine Kinase Inhibitors (TKIs) have transformed outcomes for chronic myeloid leukemia patients. However, their bioavailability can be reduced when co-administered with Acid-Reducing-Agents (ARAs) which occur in up to 1 in 2 patients. This may compromise efficacy and increase cost of care.

Objective: We used a US-claims database to assess the cost impact of concomitant use of TKIs with ARAs over 24 months.

Design, setting and participants: The Merative claims database identified patients with a CML code and 6 months data before and 24 months after starting a TKI. These were divided into TKI-Only and TKI-ARA cohorts. Hospitalization, readmission, and ER visit rates were analyzed and the total cost of care computed for the two cohorts over a period of 24 months, entropy balancing was used to adjust for covariates.

Results: 2,630 patients were identified, including 1,913 in TKI-Only (73%) and 712 in TKI-ARA (27%) cohorts. In TKI-Only *vs* TKI-ARA cohorts, hospitalization rates were 27% *vs* 39%, readmission rates 14% *vs* 26%, and ER visit rates 48% *vs* 59%, respectively. Total Cost of Care Per Patient Per Month (PPPM) for 24 Months was $10,286 in TKI-Only *versus* $12,950 in TKI-ARA. The respective cost with commercial insurance was $11,353 *vs* $15,444. In TKI-Only *vs* TKI-ARA hospitalization, outpatient drug and outpatient procedure PPPM costs were $3,965 *vs* $6,331, $7,799 *vs* $8,283, and $1,391 *vs* $2,176, respectively.

Conclusion: Concomitant use of a TKI and ARA is associated with increased total cost of care in CML. TKI and ARA-comedication was also associated with increased hospital admissions, readmissions within 30 days and increased ER visits.

Keywords: Acid-reducing-agents; Tyrosine kinase inhibitor; Chronic myeloid leukemia; Health care cost; Health care resource utilization; Real world evidence

Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative disease with a incidence of approximately 1-2 cases per 100,000 people annually in the US and accounts for about 15% of all adult leukemias [1]. The disease predominantly affects older adults, with a median age at diagnosis of around 64 years [1]. Advances in treatment, particularly with the advent of Tyrosine Kinase Inhibitors (TKIs), have significantly improved survival rates, turning CML into a manageable chronic condition for many [2]. As a result, the prevalence of CML in remission is increasing, with more patients living longer [3]. The hallmark of CML is the presence of the Philadelphia chromosome, a balanced reciprocal translocation between the long arms of 9 and 22 chromosomes [t (9; 22) (q34; q11)] [4]. This translocation creates the BCR-ABL fusion gene, encoding an aberrant tyrosine kinase that drives leukemic cell proliferation [5]. The direct causal relationship between CML and this well-defined genotypic anomaly afforded the development of therapies, TKIs, to target this abnormal kinase, inhibiting its activity and thereby controlling the disease [6]. The first TKI, imatinib (Gleevec), was introduced in the clinics in 2001 and represented a paradigm shift in CML treatment [7,8].

Clinical trials demonstrated remarkable efficacy, with most patients achieving complete hematologic and cytogenetic responses [9]. Imatinib transformed CML from a disease with a median survival of three to five years to one where patients could anticipate near-normal life expectancy with continuous treatment [9]. Following imatinib, second-generation TKIs such as dasatinib (Sprycel) and nilotinib (Tasigna) were developed [10]. These drugs offer several advantages, including greater potency against the BCR-ABL kinase and efficacy against some imatinib-resistant mutations [10]. Studies have shown that dasatinib and nilotinib can induce faster and deeper molecular responses compared to imatinib [10]. While the 2nd generation

TKIs have some advantages, their solubility is significantly influenced by pH, which can impact their absorption and bioavailability resulting in a negative impact on disease control [11-13]. Therefore, conditions that increase gastric pH, such as the use of Proton Pump Inhibitors (PPIs) or other Acid Reducing Agents (ARAs), can reduce solubility and, consequently, the bioavailability potentially leading to suboptimal therapeutic levels. One retrospective registry study demonstrated a 15% reduction in 5-year overall survival in CML patients taking ARAs with a TKI [14]. Therefore, the concomitant use of ARAs with a TKI should be avoided [15].

Despite this, the concomitant use of TKIs and ARAs is common in clinical practice due to the high prevalence of gastroesophageal reflux disease and peptic ulcer disease among cancer patients [16,17]. Studies indicate that up to 50% of all cancer patients receiving TKIs are also prescribed ARAs with potentially more patients using over the counter preparations [15].

Despite the negative impact of concomitant TKIs and ARAs on disease control, data examining any negative impact in terms of healthcare resource utilization in CML-patients is lacking. In this study, we analyzed the Merative Research claims database to estimate the potential impact of concomitant prescribing of TKIs and ARAS vs TKIs alone on the total cost of care per patient over a 24-month period.

Methodology

The Merative Research Database is a comprehensive and longitudinal source of healthcare data bringing together claims resources capturing medical, hospital, prescription, and demographic data. The closed claims data derived from health insurance providers in the 2006-2023 time period were utilized to identify adult patients with an ICD-10 CML code C92.1X or an ICD-9 CML code 205.1X, and at least 1 paid and dispensed claim for a CML-Indicated TKI. Each patient was required to have continuous enrollment (CE) 6 months before and 24 months after the date of first TKI prescription (TKI Index Date) **(Figure 1)**.

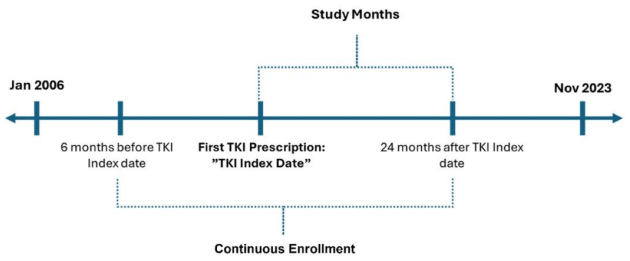

Figure 1: Study design.

Two sub-cohorts of patients were considered: 1) the TKI-only cohort, including patients who were prescribed only TKI and 2) the TKI-ARA cohort, comprising of patients who were concomitantly prescribed TKI and ARA at any time. Entropy balancing was used to balance the distribution of covariates between the two sub-cohorts [18]. Entropy balancing is a reweighting method which employs a mathematical optimization approach to reweight data to adjust for covariates ensuring exact covariate balance between treatment and control groups. This method adjusts covariates such as age, gender, and health status to achieve balance across multiple moments like mean, variance and skew. Unlike propensity score matching, which pairs individuals based on similarity and may exclude unmatched cases, entropy balance reweights the entire dataset, retaining all individuals. This comprehensive inclusion enhances the robustness of statistical inferences by preserving sample size and minimizing data loss, while allowing for different types of treatment groups including binary, continuous and multinomial. This allows comparisons between two or more treatment groups [19].

The two cohorts were balanced for age at index, sex, insurance, region, initiation with 1st or 2nd generation TKI - and Elixhauser Comorbidity Index (ECI) score. ECI, used to assess the comorbidity burden with a stratification into five categories from negligible to severe, is highly adaptable to administrative claims data, making it ideal for retrospective observational studies where detailed clinical variables may be lacking. The observations were re-weighted so that the distribution of covariates in each group was as similar as possible, subject to mean and variance. The Cost of Care and Health Care Resource Utilization (HCRU) analyses were adjusted for inflation and reported in 2023 dollars paid to providers. The costs are reported in total cost Per Patient Per Month (PPPM), both for patients with codes and normalized over total patient study cohort. Hospitalization readmission and total cost of care were analyzed by Major Diagnostic Categories (MDC) codes, Revenue Codes, Diagnosis Related Groups (DRG) codes and by Site of Service. Emergency room (ER) visits were identified using revenue code, site of service or observation status Current Procedural Terminology (CPT) codes.

Results

2,630 Adult TKI Patients with a CML Code and fulfilling the criteria of CE 6 months before and 24 months after TKI Index Date were identified (demographics are presented in **Supplementary Table 1** in the Supplementary Materials). Of these, 1,918 (73%) were in the TKI-Only cohort and 712 (27%) in the TKI-ARA cohort. In the 24 months following the TKI Index date, 27% of patients in TKI-Only were hospitalized compared to 39% of patients in TKI-ARA cohorts **(Figure 2a)**. Hospitalizations per 1,000 cohort patients per year were 2.1 times higher for patients in the TKI-ARA cohort (256 *vs* 530). Of patients who required hospitalization, 14% of TKI-Only patients required readmission within 30 days, compared to 26% of TKI-ARA patients, a 2.6-fold increase **(Figure 2b)**. 48% of TKI-Only patients had an ER visit, compared to 59% of patients on TKI-ARA. ER visit days per 1,000 cohort patients per year were 1.6-fold higher for TKI-ARA patients at 749 *vs* 1,169, **(Figure 2c)**. The total cost of care included inpatient services, outpatient procedures, outpatient drugs and long-term care. The total mean cost per patient over the 24-month period was $246,872 for TKI-Only patients and $310,805 for TKI-ARA patients, an average cost per month of $10,286 *vs* $12,950 respectively **(Figure 3)**. This difference was even greater when analyzing patients with commercial insurance with a PPPM cost of $11,354 *vs* $15,444 **(Figure 3)**.

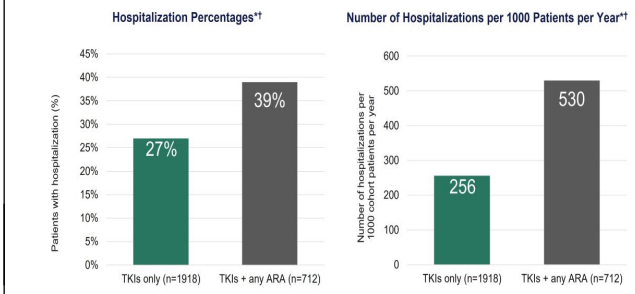

Figure 2a: Hospital admission rates during the 24 months following TKI index date. **Note:** *Cohorts were balanced and controlled for clinical factors such as age, sex, insurance, region, whether the patient started on a first-or second-generation TKI, and Elixhauser Comorbidity Index for the prior & months. Study period for hospitalization rate was 24 months following TKI index. Hospitalizations were only checked for their admittance date to be in the study period. A hospitalization that started fewer than 2 years after TKI index but continued after 2 years would be considered fully in terms of the length of stay.

Figure 2b: Readmission rates during the 24 months following TKI index date. **Note:** *Cohorts were balanced and controlled for age, sex, insurance, region, whether the patient started on a first- or second-generation TKI, and Elixhauser Comorbidity Index for the prior 6 months.
Each readmission was calculated within 30 days of the previous discharge date during the study period.

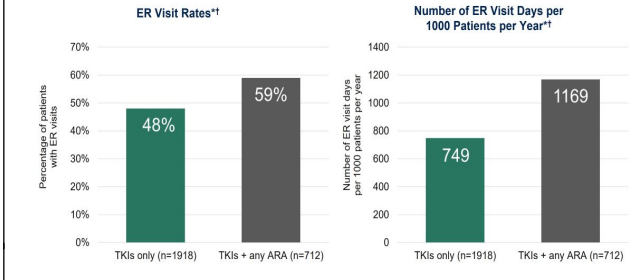

Figure 2c: Emergency Room visit rates during the 24 months following TKI index date. **Note:** Cohorts were balanced and controlled for lage, sex, insurance, region, whether the patient started on a first- or second-generation TKI, and Elixhauser Comorbidity Index for the prior 6 months. TER visits are identified using revenue code, place of service, or observation status CPT codes.

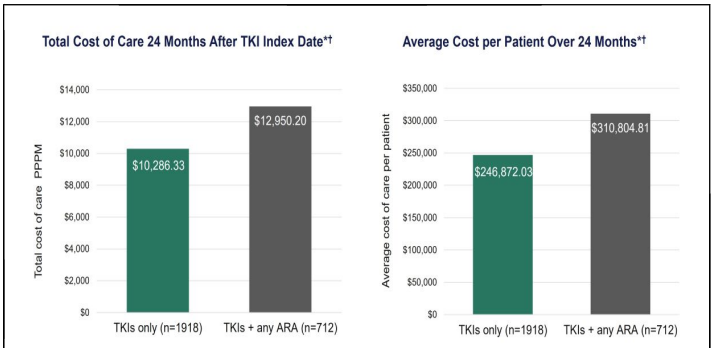

Figure 3: Cost of Care per Patient per Month during the 24 months following TKI index date. **Note:** Included in total costs: inpatient services, outpatient procedures, outpatient drugs, long-term care. All costs are weighted using entropy balancing. Patients were excluded from this analysis if they took pH-altering drugs non-concomitantly or took both PPIs and H2 antagonists.

The average total cost of hospitalizations per patient over 24 months was also higher in TKI-ARA patients, costing $151,950 *vs* $95,168, a PPPM cost of $6,331 *vs* $3,965 of hospitalized patients. The total outpatient drug costs over the 24-month period were higher in TKI-ARA patients, costing $198,806 *vs* $187,177. The average cost per patient of outpatient procedures was greater in the TKI-ARA cohort at $52,236 compared to $33,391 in the TKI-Only cohort with a PPPM cost of $2,176 *vs* $1,389.

The top 10 DRG codes showed increased PPPM cost when normalized over the cohorts in all cases. With the exception of 2, all other codes are suggestive of compromised disease control in TKI-ARA patients **(Figure 4)**. The highest cost was for allogeneic bone marrow transplant at $6312 *vs* $8952 per patient over the 24-month time period in TKI-Only vs TKI-ARA ($263 *vs* $373 PPPM) **(Table 1)**.

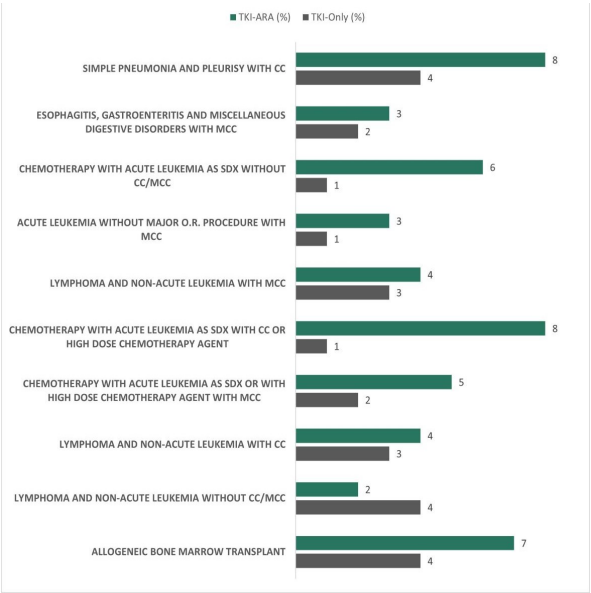

Figure 4: Top 10 Diagnosis related codes according to ARA-comedication.

Table 1: Top 10 DRG codes and PPPM cost when normalized over cohort in all cases.

Top 10 DRG codes	TKI-Only	TKI-ARA	Increase in Cost (%)
Allogenic bone marrow transplant	$262.73	$372.77	41.9%
Lymphoma and non-acute leukemia without CC*/MCC**	$16.46	$206.65	1155.5%
Lymphoma and non-acute leukemia with CC*	$16.74	$149.97	795.9%
Chemotherapy with acute leukemia as SDX or with high dose chemotherapy agent with MCC*	$14.78	$147.88	900.5%
Chemotherapy with acute leukemia as SDX with CC* or high dose chemotherapy agent	$6.31	$102.34	1521.9%
Lymphoma and non-acute leukemia with MCC**	$31.85	$91.94	188.7%
Acute leukemia without major O.R. procedure with MCC**	$36.18	$60.78	68%
Chemotherapy with acute leukemia as SDX without CC*/ MCC**	$4.35	$55.62	1178.6%
Esophagitis, gastroenteritis and miscellaneous digestive disorders with MCC**	$2.21	$36.29	1542.1%
Simple pneumonia and pleurisy with CC*	$8.88	$33.81	280.7%

The Total Cost of Care by MDC Code was also assessed. The highest PPPM cost when normalized across the cohort was for the myeloproliferative disease code. The PPPM costs were $942 for TKI-Only patients *vs* $2,354 for TKI-ARA patients, translating to a 2.5-fold difference.

Discussion

The detrimental effects of Acid-Reducing Agents (ARAs) on the efficacy of Tyrosine Kinase Inhibitors (TKIs) pose a considerable obstacle in the treatment of Chronic Myeloid Leukemia (CML). For any cancer therapy to be effective, it is imperative that the active pharmaceutical ingredient reaches the tumor site in adequate concentrations consistently. However, the pH-sensitive absorption characteristics of many TKIs make them vulnerable to alterations in gastric pH induced by the concurrent use of ARAs [20]. Consequently, this interaction has necessitated restrictions on the co-administration of ARAs with TKIs, either by requiring careful timing of medication or by avoiding concomitant use entirely due to the resulting negative effects on bioavailability and the risk of diminishing clinical efficacy [20]. Despite these limitations, it has been observed that approximately one-third of patients with CML undergoing TKI therapy are also prescribed ARAs [14]. This phenomenon may stem from the significant need for ARAs among cancer patients, and/or may reflect a lack of awareness regarding their potential impact on therapeutic outcomes and limited alternatives in treatment regimens [17]. While there are no randomized trials to investigate the impact of ARA use on clinical outcomes, multiple studies have suggested a negative impact on outcomes with concomitant ARA use across multiple cancers which is most likely driven by the reduction in solubility with increased pH and a consequent reduction in bioavailability [12, 21-25]. A recent Swedish registry study demonstrated a 15% reduction in overall survival in CML patients taking TKI's with PPIs [14]. In a retrospective study of 12,538 patients with lung cancer, renal cell cancer, CML, liver cancer, or pancreatic cancer, TKI-PPI use decreased survival at 90 days (hazard ratio, 1.16; 95% confidence interval, 1.05-1.28) and at 1 year (hazard ratio, 1.10; 95% confidence interval, 1.04-1.18)[21]. In a cross-sectional study carried out in 4 cancer centers in France, more than one quarter of the patients used PPIs. Almost one third of those treated were suspected to have reduced efficacy if taken concomitantly with TKIs [16].

While there appears to be a clear pharmacokinetic and clinical rationale for concern over the concomitant use of TKIs with ARAs, there is little data exploring the impact on cost of care for these patients and healthcare systems. Our analysis explored this in a real world setting and the results are consistent with the reported clinical data, suggesting a greater likelihood of hospital admission related to compromised disease control in CML patients taking ARAs compared to patients on TKIs alone. This leads to a less favorable clinical outcome, an increased requirement for health resource utilization and, therefore, an increase in cost of care. The underlying cause may be a suboptimal exposure to the TKI highlighting the importance of adequate absorption and bioavailability for optimal disease control. This hypothesis is supported by our data, observing a PPPM of myeloproliferative disorder according to MDC coding being 2.5-fold higher for patients co-medicated with a TKI and an ARA, suggesting poorer disease control with comedication.

Our data provides additional important findings of the impact on patients and healthcare systems. As ARA-comedicated patients still have very good outcomes despite the significant drug-drug interaction and bioavailability challenges, there can be a failure to appreciate the suboptimal outcomes. Consequently, the overall patient journey will likely be much more difficult and costly. Understanding the impact on hospitalizations is important as it can help to explain the broader impact beyond the influence on response rates and indicates an understanding of the potential impact on patient quality of life.

The surprising aspect of our claims data is the scale of the difference observed. An observed 2.1-fold increase in hospitalizations per 1,000 cohort patients per year in patients on concomitant ARAs highlights the scale of the issue and suggests a more challenging path for these patients. The reasons for admission based on DRG codes suggest that poorer disease control is a key driver for healthcare intervention. An interesting observation was that one of the highest PPPM cost was for Allogeneic Bone Marrow Transplant (ABMT) at $263 *vs* $373 in TKI-Only *vs* TKI-ARA. This may also be suggestive of poorer disease control as ABMT, per guidelines, is recommended for patients who have progressed beyond the chronic phase and require escalation in treatment [26]. The observation of the highest PPPM cost, myeloproliferative disease code, further supports this at $942 in TKI-Only patients *vs* $2,354 in TKI-ARA patients.

The utilization of a claims database in this analysis enabled the assessment of a sizeable patient cohort, accurately reflecting real-world healthcare utilization patterns while encompassing comprehensive details regarding diagnoses, procedures, medication prescriptions, and overall healthcare engagement. However, it is crucial to recognize that the primary purpose of this data collection is for billing rather than for research, thereby introducing potential inaccuracies, coding errors, and incomplete data. While claims data offers extensive insights into healthcare utilization, it inherently lacks detailed clinical information, which can impede the understanding of the clinical nuances and context of patient care. Additionally, the profiles of individuals captured in the database may reflect a disproportionate representation of certain insurance types or socioeconomic backgrounds, potentially leading to biased findings. Moreover, the inherent selection bias is evident, as the dataset includes only those individuals actively seeking healthcare services. Prescribing concomitant ARAs may indicate a higher-risk patient population, which could contribute to suboptimal outcomes.

To mitigate these concerns, entropy balancing was employed to match cohorts demographically and clinically based on age at index, sex, type of insurance, geographic region, initiation of first- or second-generation TKIs, and Elixhauser Comorbidity Index (ECI) score, thereby reducing or eliminating confounding effects through appropriate weighting. Unlike propensity score matching or inverse probability weighting, entropy balancing directly optimizes weights so that the reweighted moments (e.g., means, variances) of covariates in the control group match those in the treatment group by construction [18]. This approach avoids common pitfalls such as poor balance, loss of data due to matching, or unstable extreme weights.

One key benefit is that entropy balancing guarantees covariate balance without iterative diagnostics or tuning, enhancing internal validity and reducing confounding bias [27]. Because the weights are derived by minimizing the entropy distance from uniform weights, the method maintains sample efficiency and reduces variance inflation relative to propensity score methods [28]. Additionally, it allows for incorporating higher-order moments and interactions, increasing flexibility in modeling complex covariate distributions.

Entropy balancing is particularly advantageous when treatment assignment is non-random and baseline covariate differences are pronounced, making it a valuable tool for causal inference in health services research, economics, and epidemiology.

Additionally, the ECI score is a widely used tool for adjusting comorbidity burden in health services research and administrative claims-based studies. It captures a broad range of 30 comorbid conditions using International Classification of Diseases (ICD) codes and is particularly suited for inpatient datasets.

One key advantage is its superior predictive performance. Multiple studies have demonstrated that the ECI outperforms the Charlson Comorbidity Index in predicting inpatient mortality, length of stay, hospital costs, and readmission risk [29, 30].

Moreover, the ECI is particularly well-suited for use with administrative claims data, where diagnostic codes are available but clinical measures may be limited. It is compatible with both ICD-9 and ICD-10 coding systems, and validated algorithms exist for extracting the comorbidities efficiently, making it widely applicable in large-scale epidemiological and health services research.

Despite the inherent challenges involved in interpreting claims data, the findings of this study align closely with existing clinical evidence, indicating that the concomitant use of TKIs and ARAs is associated with poorer patient outcomes and increased healthcare costs. These outcomes may adversely affect patients' quality of life, warranting further investigation.

The recognized unmet need is clear: there is a pressing requirement for high-quality prospective clinical studies to elucidate the impact of concomitant ARAs on outcomes for patients undergoing TKI treatment. Additionally, the development of TKIs with reduced pH-dependent absorption is necessary to provide improved therapeutic options for CML patients who require ARAs. Advances in drug formulation technologies also hold promise for enhancing the bioavailability of existing TKIs in the presence of ARAs.

Furthermore, it is vital for regulatory agencies and clinical guidelines to integrate the latest evidence regarding the interactions between ARAs and TKIs, thereby providing unequivocal recommendations to clinicians. Lastly, these guidelines should be updated to endorse specific drugs or formulations that are tailored to patient needs, ensuring optimal therapeutic experiences and outcomes.

Declaration of Funding

This research was funded by Xspray.

Acknowledgments

The authors would like to acknowledge Olof Harlin and Per Anderson for their input, guidance and editorial assistance to the authors during preparation of this manuscript.

References

1. NCI. Cancer Stat Facts: Leukemia-Chronic Myeloid Leukemia (CML). Accessed 13-DEC-2024.
2. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, et al. (2020) European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 34: 966-984.
3. Jabbour E, Kantarjian H (2020) Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol 95: 691-709.
4. Rowley JD (1973) Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 243: 290-293.
5. Goldman JM, Melo JV (2003) Chronic myeloid leukemia--advances in biology and new approaches to treatment. N Engl J Med 349: 1451-1464.
6. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, et al. (2001) Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344: 1031-1037.
7. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 376: 917-927.
8. Waller CF (2014) Imatinib mesylate. Recent Results Cancer Res 201: 1-25.
9. Moen MD, McKeage K, Plosker GL, Siddiqui MA (2007) Imatinib: a review of its use in chronic myeloid leukaemia. Drugs 67: 299-320.
10. Osman AEG, Deininger MW (2021) Chronic Myeloid Leukemia: Modern therapies, current challenges and future directions. Blood Rev 49: 100825.
11. Tian X, Zhang H, Heimbach T, He H, Buchbinder A, et al. (2018) Clinical pharmacokinetic and pharmacodynamic overview of nilotinib, a selective tyrosine kinase inhibitor. J Clin Pharmacol 58: 1533-1540.
12. Budha NR, Frymoyer A, Smelick GS, Jin JY, Yago MR, et al. (2012) Drug Absorption Interactions Between Oral Targeted Anticancer Agents and PPIs: Is pH-Dependent Solubility the Achilles Heel of Targeted Therapy? Clin Pharmacol Ther 92: 203-213.
13. Andersson P, Brisander M, Liljebris C, Jesson G, Lennernäs H (2024) Severe impact of omeprazole timing on ph-sensitive dasatinib absorption: Unveiling substantial drug–drug interaction. J Clin Pharmacol 65: 588-597.
14. Larfors G, Andersson P, Jesson G, Liljebris C, Brisander M, et al. (2023) Despite warnings, co-medication with proton pump inhibitors and dasatinib is common in chronic myeloid leukemia, but XS004, a novel oral dasatinib formulation, provides reduced pH-dependence, minimizing undesirable drug-drug interactions. Eur J Haematol 111: 644-654.
15. Yu G, Zheng QS, Wang DX, Zhou HH, Li GF (2014) Drug interactions between tyrosine-kinase inhibitors and acid suppressive agents: More than meets the eye. Lancet Oncol 15: e469-e470.
16. Raoul JL, Guérin-Charbonnel C, Edeline J, Simmet V, Gilabert M, et al. (2021) Prevalence of proton pump inhibitor use among patients with cancer. JAMA Netw Open 4: e2113739.
17. Smelick GS, Heffron TP, Chu L, Dean B, Weat DA, et al. (2013) Prevalence of Acid-Reducing Agents (ARA) in cancer populations and ara drug–drug interaction potential for molecular targeted agents in clinical development. Mol Pharm 10: 4055-4062.
18. Hainmueller J (2012) Entropy balancing for causal effects: A multivariate reweighting method to produce balanced samples in observational studies. Political Analysis 20: 25-46.
19. Chen R, Chen G, Yu M (2023) Entropy balancing for causal generalization with target sample summary information. Biometrics 79: 3179-3190.
20. Hussaarts K, Veerman GDM, Jansman FGA, van Gelder T, Mathijssen RHJ, et al. (2019) Clinically relevant drug interactions with multikinase inhibitors: A review. Ther Adv Med Oncol 11.
21. Sharma M, Holmes HM, Mehta HB, Chen H, Aparasu RR, et al. (2019) The concomitant use of tyrosine kinase inhibitors and proton pump inhibitors: Prevalence, predictors, and impact on survival and discontinuation of therapy in older adults with cancer. Cancer 125: 1155-1162.
22. Chu MP, Ghosh S, Chambers CR, Basappa N, Butts CA, et al. (2015) Gastric Acid suppression is associated with decreased erlotinib efficacy in non-small-cell lung cancer. Clin Lung Cancer 16: 33-39.
23. Fang YH, Yang YH, Hsieh MJ, Hung MS, Lin YC (2019) Concurrent proton-pump inhibitors increase risk of death for lung cancer patients receiving 1st-line gefitinib treatment - a nationwide population-based study. Cancer Manag Res 11: 8539-8546.
24. Du X, Liu W, Chen K, Wang Z, Li X, et al. (2022) Impact of the gastric acid suppressant use on the safety and effectiveness of egfr-tkis: A systematic review and meta-analysis. Front Pharmacol 13: 796538.
25. Xia J, Zhu J, Li L, Xu S (2022) Concomitant gastric acid suppressants on the survival of patients with non-small-cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors: A meta-analysis. Int J Clin Pract 2022: 3102641.

26. Shah NP, Bhatia R, Altman JK, Amaya M, Begna KH, et al. (2024) Chronic myeloid leukemia, Version 2.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 22: 43-69.

27. Hainmueller J, Xu Y (2013) Ebalance: A stata package for entropy balancing. Journal of Statistical Software 54: 1-18.

28. Ho DE, Imai K, King G, Stuart EA (2007) Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Political Analysis 15:199-236.

29. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ (2009) A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 47: 626-633.

30. Quan H, Sundararajan V, Halfon P, Fonge A, Burnand B, et al. (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 43: 1130-1139.