ORIGINAL RESEARCH

Investigating Real-World Tolerance and Dose Reductions of Oncology Multikinase Inhibitors in a VA Population

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Background: Oral multikinase inhibitors (MKIs) are widely used and effective targeted therapies for patients with cancer. These agents can have substantial drug-drug interactions and adverse effects (AEs), which can make them difficult to tolerate. This study sought to evaluate the real-world tolerance of MKIs prescribed by the hematology/oncology clinic at the Veterans Affairs North Texas Health Care System (VANTHCS) to guide clinicians in the selection of starting doses and in setting expectations for the management of dose titrations.

Methods: A retrospective chart review of veterans managed by the VANTHCS hematology/oncology clinic with a prescription for axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, or sunitinib was conducted for patients treated from January 1, 2014, to October 31, 2024. The primary outcome was the evaluation of MKI tolerance through determining the relative dose intensity (RDI) and mean and median time on therapy. Secondary outcomes included rates of AEs and adjustments in doses.

Results: One hundred seventy veterans with 208 MKI prescriptions met the study inclusion criteria. The overall combined mean MKI RDI was 67.5%. Individual mean RDIs were 71.0% for axitinib, 59.6% for cabozantinib, 63.7% for lenvatinib, 82.3% for pazopanib, 61.2% for regorafenib, 49.0% for sorafenib, and 85.5% for sunitinib. The mean and median time on therapy for all MKIs (excluding days of therapy that were held) was 155 and 95 days, respectively. There were 376 AEs. Eighty-one prescriptions (38.9%) started at the indicated dose and 127 prescriptions (61.1%) were initiated at a reduced dose because of baseline concerns. Across both groups, 90 prescriptions (43.3%) required further dose reduction during therapy.

Conclusions: Oncology MKI therapies used at VANTHCS were difficult for veterans to tolerate and ultimately led to suboptimal dosing. Clinicians may use these data to guide decision-making when initiating and managing MKI agents in this population.

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The US Department of Veterans Affairs (VA) annually treats around 450,000 veterans with cancer and diagnoses an additional 56,000.[1,2] Oral multikinase inhibitors (MKIs) are widely used as targeted therapies for many different malignancies. Despite the ease of oral administration, these agents are often accompanied by significant adverse effects (AEs) and drug-drug interactions.[3,4] Common AEs include hypertension, cutaneous reactions, gastrointestinal disturbances, proteinuria, and fatigue. Some serious outcomes that may occur are myocardial infarction, thrombosis, nephrotic syndrome, hemorrhage, hepatotoxicity, and gastrointestinal events.[5,6] Due to poor tolerability of these AEs, dose reductions, frequent therapy holds, and discontinuation of therapy may occur.

The US Food and Drug Administration recognizes dosing challenges with novel therapies and has created the Oncology Center of Excellence (OCE) Project Optimus initiative to reform dose optimization in oncology drug development. The initiative aims to shift the focus from establishing dose regimens based on the maximum tolerated doses of cytotoxic chemotherapeutics to an emphasis on maximum efficacy, safety, and tolerability, which better reflect real-world dosing.[7,8]

MKIs can be challenging to manage because of the frequent toxicity-related dose reductions, interruptions, and discontinuations. In a multicenter retrospective study, Schnadig et al investigated dosing characteristics of first-line sunitinib for advanced renal cell carcinoma (RCC) and found that, among 114 patients who experienced AEs while taking sunitinib, 39.5% had dose reductions, 5.3% delayed therapy, 18.4% required additional supportive medications, and 22.8% discontinued sunitinib.[9] Overall survival and median progression-free survival of these patients were lower than reported by Motzer et al in a phase 3 clinical trial.[10] Schnadig et al concluded that patients treated with sunitinib for RCC in the community setting required more frequent dose reductions and had less time on therapy compared with patients in clinical trials, which ultimately impacted clinical outcomes.[9]

At the VA North Texas Health Care System (VANTHCS), patients with cancer have difficulty tolerating MKIs and often require dose alterations and/or discontinuation because of drug intolerance rather than discontinuation due to progression. Frequent dose adjustments for toxicity management can place more strain on patients and health care resources because of additional appointments, clinician time, and emergency department visits. Escalating drug costs can also cause concern when prescription doses are unused or changed frequently.

To capture and quantify prescribing practices and dose adjustments, this study evaluated the tolerability of MKIs at VANTHCS. This analysis may also guide clinicians in the selection of

starting doses as well as dose titration expectations to optimize MKI therapy.

METHODS

This single-center, retrospective chart review analyzed patients receiving oral oncology MKIs for various malignancies at VANTHCS between January 1, 2014, and October 31, 2024. Participants included adults aged ≥ 18 years with a prescription for axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, or sunitinib initiated by the hematology/oncology service at VANTHCS. Patients were included if they had follow-up documentation with the hematology/oncology service and/or other VANTHCS clinicians outlining their course of therapy after MKI initiation. Patients were excluded if they did not have sufficient follow-up documentation (eg, transferred care to a non-VA health care practitioner [HCP], moved to another VA health care system), were enrolled in clinical trials, or were prescribed an MKI from a Care in the Community (CITC) prescriber. Electronic health record review and data collection were performed using the VA Computerized Patient Record System and Research Electronic Data Capture. Data were collected from the time of initiation to cessation of therapy and included information regarding therapy changes, progressive disease, and date of death, when available. Data collected included age, sex, race, comorbidities, date of death, type of malignancy and subtypes, cancer stage, MKI used (ie, drug, dose, frequency, schedule, and indication), dates of medication changes (ie, start, adjustment, hold, discontinuation), concurrent antineoplastic treatments, and AEs documented at times of dose change or interruption.

The primary outcome was MKI tolerance determined using relative dose intensity (RDI) and mean and median time on therapy. Two methods are used to calculate RDI that vary in how they approach time on therapy as outlined in Hawn et al.[11] This study used method 2, which accounts for holds in therapy by comparing the actual duration of treatment with the duration expected according to treatment protocol. Method 1 compares the prescribed dose with the administered dose and does not adjust for holds.[11] Using method 2, the RDI in this study was calculated by dividing the total actual dose given by the total indicated dose for the malignancy being treated, which accounts for duration of treatment.

The total actual dose was the strength, frequency, and days on therapy for each time frame of treatment multiplied together. This method accounted for all dose adjustments and time periods of treatment holds, including patient self-adjustments, prescriber-directed adjustments, and nonadherence determined by HCP documentation and/or prescription data. Similarly, the indicated total dose was calculated by multiplying the indicated strength, frequency, and all days that treatment should have occurred (time from start to finish). Indicated doses were derived from the prescribing information for each malignancy with the exception of sunitinib, for which the off-label dose of 37.5 mg daily was considered a full dose.[12,13] The total indicated dose for axitinib was calculated by considering the dose escalation schedule from the prescribing information.

$$RDI = \frac{\sum_{i=1}^{n} (Actual\ Dose_i \times Actual\ Frequency_i \times Days\ Administered_i)}{Indicated\ Dose \times Indicated\ Frequency \times Total\ Days\ Indicated}$$

i=an instance of the specific dose, frequency, and days administered

Patients who required dose reductions due to renal/hepatic impairments or drug-drug interactions had their total indicated dose calculated using dose adjustments listed in the prescribing information. The mean RDI for each MKI agent was calculated by averaging the RDI for each prescription. The overall combined mean RDI included the means of all the MKIs reviewed to avoid skewing the results toward an MKI with more prescriptions. RDIs were also calculated for each cancer type for each agent. Additional descriptive secondary outcomes included rates of AEs and adjustments in doses.

RESULTS

Electronic data extraction identified 278 patients with 366 MKI prescriptions, of which 108 veterans with 158 MKI prescriptions were excluded. The top reason for exclusion was patients managed through CITC. Ultimately, 170 veterans with 208 MKI prescriptions managed by the VANTHCS hematology/oncology clinic were included (Table 1). Among patients receiving MKIs, the mean age was 72.7 years, 98% were male, and 99% had metastatic disease.

The overall combined mean MKI RDI was 67.5% using method 2 and ranged from 85.5% for sunitinib to 49.0% for sorafenib (Figure 1). Additional information regarding mean and median RDIs using method 2 is shown in Figure 1 and further subdivided by cancer type in Table 2. Median RDIs overall were similar to mean RDIs for most agents. Figure 2 indicates the mean and median time on therapy, reflecting time on therapy excluding days therapy was held. The overall combined mean and median days on therapy for all MKIs were 155 days and 95 days, respectively. Mean time on therapy depended

TABLE 1. Baseline Patient Characteristics (N = 170)

	Result
Age, mean, y	72.7
Sex, male, No. (%)	167 (98.2)
Race, No. (%)	
White	109 (64.1)
Black or African American	40 (23.5)
Other[a]	21 (12.4)
Cancer type, No. (%)	
Hepatocellular carcinoma	83 (48.8)
Renal cell carcinoma	64 (37.6)
Colorectal	6 (3.5)
Neuroendocrine	5 (2.9)
Thyroid	5 (2.9)
Sarcoma	4 (2.4)
Gastrointestinal stromal tumor	3 (1.8)
Medication, No. (%)	
Axitinib	26 (12.5)
Cabozantinib	28 (13.5)
Lenvatinib	14 (6.7)
Pazopanib	35 (16.8)
Regorafenib	9 (4.3)
Sorafenib	78 (37.5)
Sunitinib	18 (8.7)

[a]American Indian/Alaska Native, Native Hawaiian or Pacific Islander, Asian, or unknown/not reported.

on the agent used and ranged from 35 days (regorafenib) to 237 days (cabozantinib).

Of 208 MKI prescriptions, 127 (61.1%) were initiated at a reduced dose due to baseline concerns for tolerance such as performance status, frailty, and prior intolerance of other treatments. Eighty-one prescriptions (38.9%) were initiated at their indicated doses. Ninety prescriptions (43.3%) required dose reductions during treatment. Some MKI prescriptions had multiple dose increases and decreases, which is why RDI more accurately reflects dose adjustments. A total of 376 AEs that contributed to a dose adjustment, hold, or discontinuation occurred across all MKI prescriptions. The most common AEs were 82 failure-to-thrive events (21.8%) (fatigue, malaise, loss of appetite, reduced mobility, global decline), 79 gastrointestinal events (21.0%) (nausea, vomiting, diarrhea, abdominal pain), 62 dermatologic events (16.5%) (rash, hand-foot skin reactions, allergic response), 61 hepatic dysfunction events (16.2%) (liver enzyme elevations, hyperbilirubinemia), 40 cardiovascular events (10.6%) (hypertension, heart failure exacerbations, edema), and 33 renal dysfunction events (8.8%) (acute kidney injury, proteinuria) (Appendix 1).

DISCUSSION

The mean RDI of MKI prescriptions used in the veteran population at VANTHCS was about two-thirds of the indicated dose. These results indicate that most veterans required dose reductions and/or holds due to concerns over initial tolerance/performance status, worsening clinical condition, and/or intolerable AEs attributed to treatment. A retrospective study conducted by Denduluri et al suggested that an RDI of < 85% is a clinically meaningful reduction for traditional chemotherapy based on previous literature.[14] However, it is less clear what RDI should be expected specifically for MKIs in real-world populations. The MKI phase 3 approval trials in RCC for axitinib, lenvatinib, and sunitinib found median RDIs of 89.4%, 69.6% to 70.4%, and 83.9%, respectively. Each trial cited dose reductions most commonly as the result of treatment-related AEs.[15,16]

Studies on the impact of RDIs on survival outcomes found that higher RDIs may improve overall and progression-free survival. Retrospective studies inspecting lenvatinib in hepatocellular carcinoma (HCC) indicated that an RDI > 70% in the initial 4 weeks resulted in favorable survival outcomes.[17] Similarly, a retrospective study investigating sunitinib in RCC found that an RDI > 60% conferred favorable survival outcomes.[18] Alghamdi et al noted that patients taking sorafenib for HCC who had RDI > 50% had a favorable trend in survival characteristics. Interestingly, the study found an RDI of 50% to 75% appeared to have better survival than an RDI > 75%.[19] The authors of these studies hypothesized that additional dose reductions allowed for longer total time on therapy due to improved tolerability.[17-19]

This analysis found that the RDIs for most MKI agents at VANTHCS were < 85% and lower than the RDIs found in other review articles and phase 3 trials, with the exceptions of pazopanib in thyroid cancer and sunitinib in gastrointestinal stromal tumor (GIST), thyroid cancer, and neuroendocrine cancer. The reasons for the lower RDIs in this study are likely multifactorial, reflecting patient population characteristics, off-label dosing practices, and HCP experiences with these agents. Many veterans have chronic comorbidities that could contribute to reduced performance status and ability to tolerate these therapies. Despite attempts to preemptively reduce doses for patients and account for potential impaired tolerance, there were patients who required further dose reductions in our study.

Failure to thrive was the most common AE leading to dose adjustment or discontinuation, which illustrates the extensive effects these agents have on patient functioning in a real-world

population. Notably though, the RDI for sunitinib was higher in this population because about half of patients were dosed using the off-label recommendation, whereas the prescribing information recommends a more intensive 6-week dosing cycle for certain cancer types.[12,13,20] Sorafenib was also often dose-adjusted based on a pharmacokinetic study of sorafenib in renal/hepatic dysfunction, and the RDI likely reflects the off-label prescribing pattern.[21]

Patients with thyroid cancer were found to have higher RDIs compared with those receiving the same agents for other cancer types. Improved tolerability of MKIs in thyroid cancer may be due to a generally more tolerable disease course. Thyroid cancer is the most common cancer in individuals aged < 40 years, a population that is often more robust with fewer comorbidities. Moreover, the 5-year relative survival rate for thyroid cancer remains > 98%.[22] This rate is in contrast to those for other cancer types such as HCC, with a 5-year relative survival rate of only 15%.[23]

It is challenging to compare the mean and median times on therapy found in this study with those in current literature, as this review included multiple different cancer types for each agent. However, the numbers are generally lower than durations of therapy found across the different disease states and further emphasize the difficulty in tolerating MKIs in the VANTHCS population. Regorafenib had a short duration of time on therapy, which highlights the importance of trials like ReDOS and initiatives such as OCE Project Optimus in helping improve tolerance.[7,8,24]

Comparing our results with other studies proved challenging because the RDI calculation methods were not specified. Calculating RDIs in this study using method 1, which does not account for holds, resulted in higher RDIs (Appendix 2). Using method 1, all MKIs had RDIs < 85%, except for pazopanib in thyroid cancer (100%) and RCC (87.9%), and sunitinib in GIST (93.6%), thyroid cancer (100%), and neuroendocrine cancer (93.7%). Notably, using method 1 increased the RDI for pazopanib in neuroendocrine cancer from 5.4% to 50.0%. The low RDI was attributed to a single veteran with a long hold duration, which demonstrates the discrepancy that can occur between the 2 methods.

Limitations

The retrospective design, lack of survival outcomes, and difficulty comparing results with other literature were limitations of this study. Because survival outcomes were not evaluated, future research should seek to investigate how RDIs and dose adjustments made among MKIs can affect survival outcomes in real-world populations. This veteran population with cancer often had multiple chronic comorbidities, which may have contributed to difficulty tolerating MKIs and could have impacted results. Disease-related factors may have influenced the poor tolerance of the MKIs and were not specifically accounted for. Adjustment for comorbidities was not possible because of discrepancies and/or incomplete diagnosis codes and Eastern Cooperative Oncology Group performance status scores documented in patient charts. Therefore, we decided not to report these findings due to potential inaccuracies.

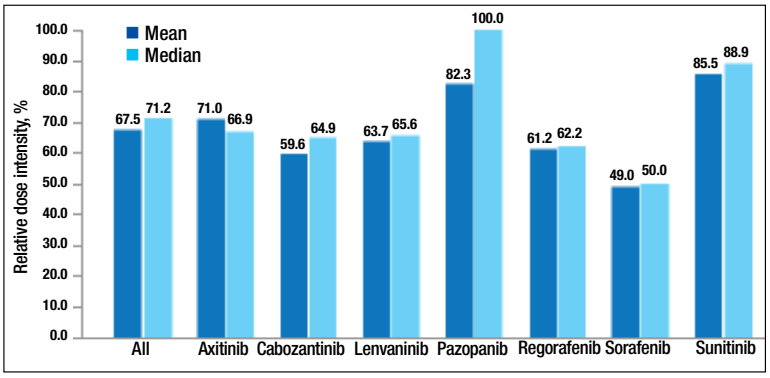

FIGURE 1. Multikinase Inhibitor Relative Dose Intensities

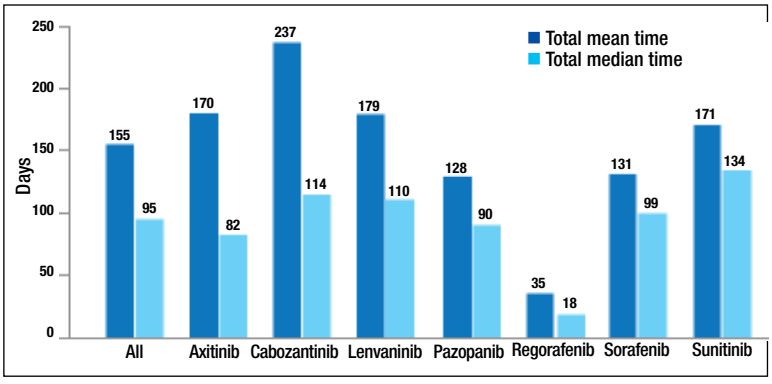

FIGURE 2. Time on Multikinase Inhibitor Therapy

CONCLUSIONS

Results of this study demonstrate that oncology MKI agents used at VANTHCS were difficult for patients to tolerate, leading to suboptimal dosing compared with indicated doses established in clinical trials and prescribing information. Clinicians may use these data to help guide clinical decision-making whenever initiating and managing MKI agents in this population. These findings reinforce that MKI agents are often difficult to tolerate in real-world practice, and indicated doses are often not achieved. Further

TABLE 2. Multikinase Inhibitor Relative Dose Intensity (Method 2)

Cancer type	Axitinib	Cabozantinib	Lenvatinib	Pazopanib	Regorafenib	Sorafenib	Sunitinib
CRC, mean (median), %	—	—	—	—	59.9 (56.1)	—	—
GIST, mean (median), %	—	—	—	—	75.0 (75.0)	—	93.3 (100)
HCC, mean (median), %	—	60.4 (62.9)	65.9 (66.7)	—	58.3 (58.3)	48.7 (50.0)	—
Neuroendocrine, mean (median), %	—	—	—	5.4 (5.4)	—	—	91.1 (100)
RCC, mean (median), %	71.0 (66.9)	59.1 (65.6)	47.8 (47.8)	84.5 (100)	—	—	80.7 (77.6)
Sarcoma, mean (median), %	—	—	—	74.8 (77.6)	—	—	57.5 (57.5)
Thyroid, mean (median), %	—	—	67.3 (75.2)	100 (100)	—	76.4 (76.4)	100 (100)

Abbreviations: CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

studies should aim to investigate the effect that various RDIs have on overall survival. Further investigation into different dosing schemes for MKIs to improve tolerability and longer-term use may also prove beneficial.

This analysis may help guide clinicians to carefully approach dosing MKI agents in the veteran population. Given the RDI and AEs, more clinicians may consider starting at lower than indicated doses with the goal to titrate up as tolerated. Additionally, the results highlight the importance of considering palliative care consults and ensuring appropriate supportive care agents are preemptively engaged and adjusted as needed. Approaching dosing and titrations cautiously may help reduce the burden of management on the health care system.

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Author disclosures

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Ethics and consent

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Veterans Affairs North Texas Healthcare System Institutional Review Board approved this study. Given retrospective nature of this article, patient consent was not required.

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APPENDIX 1. Multikinase Inhibitor Adverse Effect Rates

Adverse effect	Axitinib, % (n = 39)	Cabozantinib, % (n = 53)	Lenvatinib, % (n = 29)	Pazopanib, % (n = 55)	Regorafenib, % (n = 17)	Sorafenib, % (n = 151)	Sunitinib, % (n = 32)
Cardiovascular	10.3	9.4	13.8	12.7	0	11.3	9.4
Gastrointestinal	17.9	13.2	24.1	32.7	35.3	19.2	15.6
Dermatologic	17.9	26.4	10.3	12.7	52.9	10.6	18.8
Renal	10.3	5.7	20.7	10.9	0	7.3	9.4
Hepatic	15.4	15.1	0	9.1	11.8	25.8	3.1
Failure to thrive	23.1	20.8	27.6	16.4	0	21.2	40.6
Pulmonary or hematologic	5.1	9.4	3.4	5.5	0	4.6	3.1

APPENDIX 2. Multikinase Inhibitor Relative Dose Intensity (Method 1)

Cancer type	Axitinib	Cabozantinib	Lenvatinib	Pazopanib	Regorafenib	Sorafenib	Sunitinib
CRC, mean (median), %	—	—	—	—	64.4 (63.3)	—	—
GIST, mean (median), %	—	—	—	—	75.0 (75.0)	—	93.6 (100)
HCC, mean (median), %	—	67.5 (66.2)	71.4 (66.7)	—	58.3 (58.3)	50.4 (50.0)	—
Neuroendocrine, mean (median), %	—	—	—	50.0 (50.0)	—	—	93.7 (100)
RCC, mean (median), %	78.2 (83.3)	61.3 (66.7)	62.6 (62.6)	87.9 (100)	—	—	80.1 (75.0)
Sarcoma, mean (median), %	—	—	—	84.4 (98.3)	—	—	66.7 (66.7)
Thyroid, mean (median), %	—	—	81.7 (83.8)	100 (100)	—	88.3 (88.3)	100 (100)
Combined, mean (median), %	78.2 (83.3)	63.5 (66.4)	73.1 (73.9)	87.2 (100)	64.2 (66.6)	50.9 (50.0)	86.5 (91.2)

Abbreviations: CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

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