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REVIEW

Serum creatine kinase elevation following tyrosine kinase inhibitor treatment in cancer patients: Symptoms, mechanism, and clinical management

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Abstract

Molecular targeted tyrosine kinase inhibitors (TKIs) have produced unprecedented treatment response in cancer therapy for patients harboring specific oncogenic mutations. While the TKIs are mostly well tolerated, they were reported to increase serum levels of creatine kinase (CK) and cause muscle metabolism-related toxicity. CK is an essential enzyme involved in cellular energy metabolism and muscle function. Elevated serum CK levels can arise from both physiological and pathological factors, as well as triggered by specific drug classes. The incidence of serum CK elevation induced by a few approved TKIs (brigatinib, binimetinib, cobimetinib-vemurafenib combination [Food and Drug Administration, United States]; aumolertinib, and sunvozertinib [only approved by National Medical Products Administration, China]) were over 35%. CK elevation-related symptoms include myopathy, myositis, inclusion body myositis (IBM), cardiotoxicity, rhabdomyolysis, rash, and acneiform dermatitis. High-level or severe symptomatic CK elevation may necessitate dose reduction and indirectly dampen TKI efficacy. This review presents an updated summary about the prevalence rate and recent research about mechanisms leading to TKI-induced serum CK elevation in cancer patients. The utility of monitoring serum CK levels for predicting TKI-induced adverse effects and their management will also be discussed.

INTRODUCTION

Tyrosine kinases (TKs) are crucial components of cellular enzymatic machinery regulating signal transduction pathways, which play a pivotal role in cell proliferation, differentiation, apoptosis, and other biological processes. Dysregulation of TK-regulated signaling is known to promote tumorigenesis.[1] Tyrosine kinase inhibitors (TKIs) are a large class of targeted therapeutic drugs that effectively suppress tumor growth and proliferation by inhibiting major oncogenic signaling pathways through the targeting of receptor or non-receptor TKs. Over the past two decades, there has been significant progress in the development of TKIs targeting specific receptors including EGFR, VEGFR, ALK, ROS1, HER2, NTRK, RET, and MET.[1] The clinical application of these TKIs in chronic myeloid leukemia (CML), gastrointestinal stromal tumor (GIST), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and other cancers, has significantly enhanced the survival and quality of life of

patients. TKIs are generally well tolerated and they exhibit a more favorable toxicity profile than traditional chemotherapeutic drugs. Nevertheless, TKIs could still produce severe adverse events (AEs) such as cutaneous reaction, paronychia, and diarrhea.[2]

Creatine kinase (CK), also known as creatine phosphokinase (CPK), is an important enzyme regulating cellular energy metabolism, muscle contraction, and adenosine triphosphate (ATP) regeneration. It catalyzes the reversible transfer of phosphate groups between creatine and ATP, thereby providing energy for muscle contraction and transport systems (Figure 1). It is usually present at low concentration in the bloodstream. Serum CK level can rise after heart attack, skeletal muscle injury, or strenuous exercise. There are three subtypes of CK, namely CK-MM (predominantly found in skeletal muscles), CK-MB (present in cardiac muscles), and CK-BB (located in brain tissues). The measurement of CK in the blood has been applied in the diagnosis of conditions associated with muscle damage. To this end, the elevation of serum CK could also occur accompanying TKI-induced adverse reactions.[1]

Elevated serum CK level is a prevalent clinical phenomenon, commonly observed due to various physiological factors, including age, gender (more obvious in males), race (more prevalent in individuals of African descent), geographical location, and strenuous exercise.[1] On the contrary, pathological elevation of CK level could indicate increased cell permeability or cellular damage in tissues containing CK, often resulting from neuromuscular disorders such as muscular dystrophy, metabolic myopathies, inflammatory myopathies, and central or peripheral nervous system disorders affecting the muscles.[1] Non-neuromuscular conditions including cardiovascular disease, endocrine disorders, metabolic abnormalities, obstructive sleep apnea, connective tissue diseases, and malignant tumors can also lead to elevated serum CK levels. Interestingly, a few widely consumed medications, including statins (cholesterol-lowering drugs), antipsychotics, antivirals, beta blockers, and colchicine alkaloids, are known to increase serum CK levels.[1]

To this end, the incidence of CK elevation induced by a few TKIs (brigatinib, binimetinib, cobimetinib, and vemurafenib) has been reported to be more than 35%, which constituted the most common reasons for discontinuation or dose reduction.[4–6] Symptoms accompanied by CK elevation includes myopathy,[7] myalgia,[8–10] inclusion body myositis (IBM),[11] cardiotoxicity,[12,13] rhabdomyolysis,[14–17] and acneiform dermatitis.[18] High-level or symptomatic CK elevation will affect patient adherence and indirectly affects the efficacy. Factors that influence the pharmacokinetics of TKIs and risk for TKI-associated CK elevation including high-dose TKI therapy,[19] polypharmacy,[20–22] drug–drug interactions (concomitant use of statins and TKI),[20–22] other co-morbidities,[23–25] and pharmacogenetic considerations.[26] This review article provides an updated summary about the propensity of CK elevation in cancer patients receiving TKI therapy and its underlying

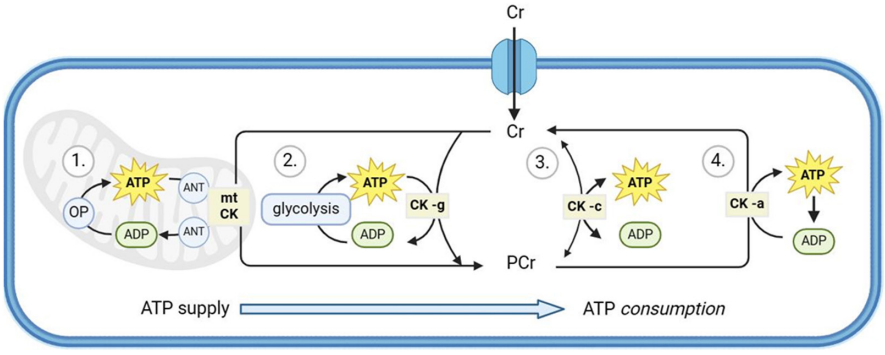

FIGURE 1 Schematic diagram illustrating the regulation of ATP production and consumption by the creatine kinase/phosphocreatine (CK/PCr) system.[3] The CK/PCr system is responsible for the temporal and spatial energy homeostasis in cells of high and fluctuating energy requirements. Creatine (Cr) enters the target cells via Cr transporter (CRT). Inside the cell, PCr/Cr and ATP/ADP equilibria are adjusted by a soluble fraction of cytosolic CK isoforms (CK-c, see (3)). Another fraction of cytosolic CK (CK-g, see (2)) is specifically coupled to glycolytic enzymes (G), accepting glycolytic ATP, while mitochondrial-CK isoforms (mtCK, see (1)) is coupled to adenine nucleotide translocator (ANT), thus accepting ATP exported from the matrix and generated by oxidative phosphorylation (OP). The contribution of both of these microcompartments to the total PCr generation depends on the cell type. The PCr thus generated is fed into the large PCr pool (up to 30 mM) that is available as a temporal or spatial energy buffer. Another fraction of cytosolic CK (CK-a, see (4)) specifically associated with subcellular sites of ATP utilization (ATPase; e.g., ATP-dependent or ATP-gated processes, ion-pumps) also forms tightly coupled microcompartments regenerating the ATP utilized by the ATPase reaction in situ in the expense of PCr. The proposed CK/PCr energy shuttle or circuit connects the various subcellular sites of ATP production (glycolysis and mitochondrial oxidative phosphorylation) with subcellular sites of ATP utilization (ATPases), via highly diffusible PCr and Cr.

mechanisms. The utility of monitoring CK elevation to predict TKI-mediated adverse effects and drug efficacy will also be discussed.

PHYSIOLOGICAL FUNCTIONS OF CK AND ITS REGULATION

Normal physiological functions of CK

As depicted in Figure 1, CK regulates the transport of ATP/ADP into and out of the mitochondria, thereby controlling energy metabolism.[27] To date, at least five isoforms of CK have been identified: three isoenzymes in the cytoplasm (CK-MM, CK-MB, and CK-BB) and another two isoenzymes (non-sarcomeric and sarcomeric) in the mitochondria.[28] An elevated CK level in the bloodstream generally indicates the occurrence of or ongoing myocyte damage.[29] Following muscle cell damage, there is a significant accumulation of free fatty acids within the cells, resulting in alterations to membrane action potential thresholds and an increase in cell membrane permeability. This leads to the direct release of muscle enzymes into the bloodstream, causing elevated serum levels of CK.[30] Microscopic examination of muscle biopsy reveals varying sizes of muscle fibers accompanied by numerous rimmed vacuoles and abnormal proliferation of tubular structures, which may serve as the pathological basis for increased levels of muscle enzymes.[31]

FACTORS LEADING TO SERUM CK ELEVATION

The mechanisms leading to CK elevation are multifactorial, which can be triggered by numerous physiological factors, systemic conditions, or various medications including TKIs. Physiological influences include race, gender, age, and exercise, with higher CK levels commonly seen in African and South Asian populations, males, and younger individuals[32] (Table 1). Systemic diseases such as malignant tumors, idiopathic inflammatory myopathies, hypertension, coronary heart disease, diabetes, and conditions such as rhabdomyolysis and hypothyroidism also contribute to raised CK levels.[34] Cachexia is present in up to 80% of patients with advanced cancer and in 60%–80% of those diagnosed with gastrointestinal, pancreatic, and lung cancers.[35] Yuko et al. compared muscle damage of cancer cachexia in mice bearing Lewis lung carcinoma/colon adenocarcinoma with that in a murine muscular dystrophy model (mdx mice). Unlike mdx mice, cachexia mice did not exhibit increase in serum CK level, and signs of regeneration were absent. In cancer cachexia, some humoral factors like TNFαand angiotensin II may block the regeneration process.[36] Medications, including statins, antipsychotics, and antiviral drugs, can lead to increased CK levels, which is often associated with muscular damage.[32]

TABLE 1 Factors contributing to serum creatine kinase (CK) elevation.

Factors	Detailed description
Non-Caucasian ethnicity	Afro-Caribbean ethnicity and muscular build[32]
Strenuous exercise	CK level may increase within 24 h of strenuous physical activity[33]
Endocrine disorders	Hypothyroidism, hyperparathyroidism[34]
Electrolyte imbalance	Low sodium, potassium or phosphate[32]
Drugs	Statins, fibrates, anti-retrovirals, beta blockers, and TKIs[32]
Muscular disorders	Inflammatory myopathies and sarcoid myopathy[34]
Miscellaneous non-muscular causes	Denervation, seizures, malignancy, and surgery[32]

CK elevation caused by non-oncology drugs

Medications are also known to be a significant and prevalent etiology for elevated serum CK levels.[1] Apart from anticancer drugs, various non-oncology drugs such as statins, antipsychotics, antiviral drugs, beta blockers, colchicine, and donepezil have also been shown to increase serum CK levels.[37]

Statins are notorious for inducing myalgia, muscle weakness, and rhabdomyolysis.[37] Approximately 5% of individuals on statin therapy may experience elevated levels of CK, typically ranging from 2 to 10 times the upper limit of normal (ULN).[38] In a prospective analysis of 2017 subjects at a single center,[1] 171 exhibited serum CK elevation (>2 times the normal value). The implicated medications included statins (46.4%), fibrates (14.3%), antiretroviral drugs (14.3%), angiotensin II receptor antagonists (10.7%), immunosuppressants (7.1%), and hydroxychloroquine (7.1%).

Serum CK elevation caused by antipsychotic drugs is also relatively common. A recent systematic review[39] reported that the incidence rate of significant CK elevation (>10 times the ULN) after taking antipsychotic drugs ranged from 2% to 7%, albeit with 83% of the patients not experiencing any significant complications. Antiviral drugs are also known to induce serum CK levels. A cohort study[40] revealed that among 475 HIV-1 infected patients

treated with raltegravir (a HIV integrase inhibitor), 11.2% experienced elevated CK levels (≥3 times the ULN), resulting in a rate of 3.8 individuals per 100 people per year. Among these cases, only 1.5% of patients with elevated CK levels reported symptoms including muscle pain and/or contractures.

Serum CK elevation triggered by TKIs

The incidence of CK elevation induced by various classes of TKIs targeting ALK, MEK1/2, B-Raf, FLT3, BCR-Abl, EGFR, VEGFR, RET, KIT, and PDGFRα (Table 2) has been reported to be more than 20% in NSCLC, melanoma, ovarian cancer, colorectal cancer, AML, CML, RCC, and GIST. In particular, brigatinib, binimetinib, cobimetinib-plus-vemurafenib combination, and gilteritinib could induce serum CK level dramatically by over 35% (Table 3). Thus, CK elevation as a biomarker may reflect the complex interplay between the therapeutic targeting of TK pathways and the unintended interference with cellular functions beyond cancer cells. TKs are not only pivotal in the pathogenesis of various cancers but they also play substantial roles in normal cellular functions, including muscle metabolism. TKIs, while designed to inhibit the aberrant signaling in tumor cells, may inadvertently impact the normal activity of kinases within muscle tissue, leading to cellular stress or damage. This off-target effect can lead to an increase in CK levels and muscle damage, which is clinically significant as it could herald the onset of adverse reactions such as myositis or cardiotoxicity. Monitoring CK levels in patients on TKIs becomes a crucial aspect of clinical management, allowing for the early detection and intervention of potential TKI-induced muscle toxicity.

Incidence of serum CK elevation by different classes of TKIs

Anaplastic lymphoma kinase (ALK) inhibitors (brigatinib, alectinib, crizotinib, and iruplinalkib)

The incidence of all-grade CK elevation by brigatinib and alectinib ranged from 16% to 70% and 10% to 29%. In phase III ALTA 1 L trial (NCT02737501), patients with ALK inhibitor-naive advanced ALK-positive NSCLC received brigatinib 180 mg/day (7-day lead-in at 90 mg once daily), and 50% of patients had CK elevation (Table 3). The incidence of Grade 3 or 4 CK elevation was 26%. Dose reduction for CK elevation occurred in 18% of patients.[41] In ALTA trial, brigatinib was applied to ALK-positive NSCLC after disease progression on crizotinib, CK elevation occurred in 17% of patients in the 90 mg group and 34% of patients in the 90 → 180 mg group. The incidence of Grade 3–4 CK elevation was 6% in the 90 mg group and 14% in the 90 → 180 mg group. Dose reduction for CK elevation occurred in 2% of patients in the 90 mg group and 9% in the 90 → 180 mg group.[19] It seems to be dose-dependent from 90 to 180 mg both in all grades and ≥Grade 3. In order to reduce the risk of early-onset pulmonary events, the phase III ATLA-3 trial introduces brigatinib at a lower dose before dose escalation.[5,68] In ATLA-3, the incidence of treatment-related CK elevation in ALK-positive NSCLC patients on brigatinib or alectinib therapy was 70% and 29%, respectively.[5] In ALTA-1 L, 17% of patients treated with crizotinib had increased CK.[41] The reasons for the differences in the clinical CK inhibitory profiles of different ALK inhibitors are not clear. A comparison between the ratio of steady-state trough unbound drug concentration (Css, trough, unbound)/ALK inhibition constant (ALK Ki) was performed. The ratios were estimated from literature-reported pharmacokinetics parameters and ALK Ki values of brigatinib (67 = 25 nM/0.37 nM),[69,70] alectinib (85 = 162 nM/1.9 nM),[71,72] and crizotinib (122 = 78 nM/0.64 nM),[73,74] respectively. Inhibition of the primary target (ALK) appears unlikely to explain the observed CK increases, as all three drugs are highly potent ALK inhibitors at their recommended doses, and there is no suggestion that the drug with the higher Css, trough, unbound/ALK Ki ratio at the therapeutic dosage was associated with greater CK increase. As such, it is possible that the differences may be explained by differential selectivity of the drugs and off-target mechanisms or other factors, pointing to areas for future research.

MEK1/2, B-Raf, PI3K inhibitors (binimetinib, encorafenib, cobimetinib, vemurafenib, selumetinib, dabrafenib, trametinib, and buparlisib)

The incidence of CK elevation induced by MEK1/2, B-Raf, PI3K TKIs was generally high following monotherapy of binimetinib (22%–81%),[4,45,46] selumetinib (76%),[48] concurrent therapy of encorafenib and binimetinib (27.1%),[43] binimetinib-plus-buparlisib combination (59.6%),[47] buparlisib-plus-trametinib combination (45.1%),[49] vemurafenib-plus-cobimetinib combination (35%),[6] and triplet therapy of encorafenib, binimetinib and cetuximab (34.3%).[44] In Columbus study (NCT01909453), while encorafenib plus binimetinib showed favorable efficacy compared with vemurafenib, 27.1% of patients in combination group had increased CK and 7.8% were

TABLE 2 Small molecule tyrosine kinase inhibitors reported to induce serum creatine kinase (CK) elevation in clinical trials.

Primary targets	TKI	Company	Trade name	Year of FDA or NMPA approval	Therapeutic indications
ALK, ROS1	Crizotinib	Pfizer	Xalkori	2011	ALK or ROS1-positive NSCLC, inflammatory myofibroblastic tumors, anaplastic large cell lymphoma
ALK, RET	Alectinib[a]	Roche	Alecensa	2015	ALK-positive NSCLC
ALK	Brigatinib[a]	Ariad Pharm	Alunbrig	2017	ALK-positive NSCLC
ALK, ROS1	Iruplinalkib	Qilu	Qixinke	2023[b]	ALK-positive NSCLC
BCR-ABL	Imatinib[a]	Novartis	Gleevec	2001	Ph + CML or ALL, aggressive systemic mastocytosis, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, GIST, myelodysplastic/ myeloproliferative disease
BCR-ABL	Dasatinib	Bristol Myers Squibb	Sprycell	2006	Ph + CML or ALL
BCR-ABL	Bosutinib[a]	Pfizer	Bosulif	2012	Ph + CML
BCR-ABL	Asciminib[a]	Novartis	Scemblix	2021	Ph + CML
B-Raf	Vemurafenib[a]	Genentech	Zelboraf	2011	$BRAF^{V600E}$ melanomas, Erdheim-Chester disease
B-Raf	Dabrafenib	GSK	Tafinlar	2013	$BRAF^{V600E/K}$ melanomas, $BRAF^{V600E}$ NSCLC, $BRAF^{V600E}$ anaplastic thyroid cancers
B-Raf	Encorafenib[a]	Array BioPharma	Braftovi	2018	Combination therapy with binimetinib for $BRAF^{V600E/K}$ melanomas
CDK4/6	Palbociclib	Parke-Davis	Ibrance	2015	Estrogen receptor- and HER2-positive breast cancers
c-MET	Merestinib	Lilly	—	Investigational	—
EGFR	Gefitinib	AstraZeneca	Iressa	2003	NSCLC with exon 19 deletions or exon 21 substitutions
EGFR	Osimertinib	AstraZeneca	Tagrisso	2015	NSCLC with exon 19 deletions or exon 21 substitutions, T790M resistance mutation
EGFR	Aumolertinib[a]	Hansoh	Ameile	2020[b]	NSCLC with exon 19 deletions or exon 21 substitutions, T790M resistance mutation
EGFR	Sunvozertinib	Dizal	Shuwozhe	2023[b]	NSCLC with ex20ins mutation
EGFR	Oritinib	Sanhome	Shengruisha	Investigational	NSCLC with T790M resistance mutation
FGFR2	Futibatinib[a]	Tiaho Pharma	Lytgobi	2022	Bile duct cancers (cholangiocarcinomas) with FGFR2 fusions or other rearrangements
FKBP12/ mTOR	Everolimus	Novartis	Afinitor	2009	HER2-negative breast cancer, pancreatic neuroendocrine tumors, RCC, angiomyolipomas, subependymal giant cell astrocytomas
FLT3	Gilteritinib[a]	Astellas Pharma	Xospata	2018	AML with FLT3 mutations
KIT, PDGFRα	Ripretinib[a]	Deciphera Pharma	Qinlock	2020	Fourth-line treatment for GIST
MEK1/2	Trametinib	GSK	Mekinist	2013	$BRAF^{V600E/K}$ melanoma, $BRAF^{V600E}$ NSCLC
MEK1/2	Cobimetinib[a]	Genentech	Cotellic	2015	$BRAF^{V600E/K}$ melanomas in combination with vemurafenib
MEK1/2	Binimetinib[a]	Array BioPharma	Mektovi	2018	Combination therapy with encorafenib for $BRAF^{V600E/K}$ melanomas
MEK1/2	Selumetinib	AstraZeneca	Koselugo	2020	Neurofibromatosis type I

(Continues)

TABLE 2 (Continued)

Primary targets	TKI	Company	Trade name	Year of FDA or NMPA approval	Therapeutic indications
PDGFRα	Avapritinib	Blueprint Medicines	Ayvakit	2020	GIST with PDGFRα exon 18 mutations
PI3K	Buparlisib	Novartis/ Adlai Nortye	—	Investigational	—
RET, VEGFR2	Cabozantinib	Exelixis	Cometriq	2012	Medullary thyroid cancer, RCC, HCC
RET	BOS172738	Daiichi Sankyo	—	Investigational	—
VEGFR1/2/3	Sorafenib	Bayer	Nexavar	2005	HCC, RCC, differentiated thyroid cancer
VEGFR2	Sunitinib[a]	Pfizer	Sutent	2006	GIST, pancreatic neuroendocrine tumors, RCC
VEGFR, RET	Lenvatinib[a]	Easai Co.	Lenvima	2015	Differentiated thyroid cancer

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

[a]TKIs that result in more than 20% increase of CK levels in phase III trials with mono or combination therapy.

[b]National Medical Products Administration (NMPA) approved.

Grade 3–4, compared with 2.2% of all grades and none of Grade 3–4 in vemurafenib alone group.[43] Binimetinib was indicated for treatment of recurrent low-grade serous ovarian carcinomas (LGSOCs; 30%–60% of these patients harbor KRAS/BRAF mutations) after at least one prior platinum-based chemotherapy but less than three prior chemotherapeutic treatments. CK elevation was occurred in 50% of patients, 26% were ≥Grade 3.[4] In phase III BEACON study (NCT02928224), 665 patients with BRAF V600E mutated metastatic colorectal cancer were assigned to receive encorafenib, binimetinib, and cetuximab (triplet therapy); encorafenib and cetuximab (doublet-therapy); or the investigators' choice of either cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil, and irinotecan) (control group). Triplet therapy or doublet therapy trended to have improved OS, ORR, and progression-free survival (PFS) compared with standard chemotherapy. CK elevation occurred in 34.3% in the triplet, 3.7% in doublet, and 7.3% in control group of all grades.[44] In two phase I/Ib studies, binimetinib alone or its combination with buparlisib (phosphatidylinositol3-kinase [PI3K] inhibitor) were investigated in patients with advanced solid tumors bearing RAS/RAF alterations. Elevated CK levels were observed in 81% and 59.6% of patients in the two studies.[46,47]

A phase III coBRIM study (NCT01689519) evaluated the combination of the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib in previously untreated unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma.[6] 35% in combination group and 3% of patients in control group had increased CK. Elevated CK level of Grade 3 or worse occurred in 12% of 247 patients in the combination group versus one (<1%) of 246 in control group.[6]

Of the 74 patients treated with selumetinib for neurofibromatosis type 11-related plexiform neurofibromas, 76% of patients experienced serum CK elevation.[48] In a phase Ib dose-escalation study, 113 patients with selected advanced solid tumors were enrolled to evaluate the combination of the pan-PI3K inhibitor buparlisib (BKM120) and MEK1/2 inhibitor trametinib. Dose-limiting toxicities (DLT) included stomatitis, diarrhea, dysphagia, and an increase in serum CK levels. 45.1% experienced elevated CK levels, with 14.2% as Grade 3–4.[49]

BCR-ABL (asciminib, bosutinib, dasatinib, and imatinib), FLT3 (gilteritinib), VEGFR1/2/3 inhibitors (sorafenib as multikinase inhibitor, sunitinib)

Serum CK elevation is frequently observed in patients treated with imatinib (20%–80%),[16,50–53] dasatinib (65%),[52] bosutinib (8%–50%),[51,52,54] asciminib (25%),[54] and gilteritinib (13.4%–37.5%).[55,56] Adenis et al.[50] conducted a prospective analysis on 155 eligible cancer patients from nine centers in France to assess the incidence of TKI-induced CK elevation. GIST was identified as the most prevalent tumor type, accounting for 105 out of 155 cases (68%). Treatments were carried out with imatinib (56%), sunitinib (14%), sorafenib (10%), HER1/2 antagonists (erlotinib, gefitinib, and lapatinib, 9%), other TKIs (10%), and imatinib-based combinations (1%). Myalgia

TABLE 3 Incidence of CK elevation by small molecule TKIs – their protein kinase targets and cancer type.

Primary targets	Reference/Trial name	TKI/drug combination	Tumor type	Trial type	N	All grade (%)[a]	≥ grade 3 (%)[a]	Dose Reduction (%)	Symptoms
ALK	Camidge et al.[41]	Brigatinib	NSCLC (ALK TKI- naive)	Phase 3	136	50	26	18[b]	Myalgia was reported in 10% patients; Musculoskeletal pain was reported in 11% patients. No grade 3 or higher myalgia or musculoskeletal pain was reported
	Gettinger et al.[19]	Brigatinib	NSCLC	Phase 1/2	79	16	5	0	Neither myalgia nor musculoskeletal pain of any grade were reported in any patients
	Gettinger et al.[19]	Brigatinib 90mg	NSCLC (progressed on crizotinib)	Phase 2	109	17	6	2	Neither myalgia nor musculoskeletal pain of any grade were reported in any patients
	Gettinger et al.[19]	Brigatinib 90 mg→180 mg	NSCLC (progressed on crizotinib)	Phase 2	110	34	14	9	Neither myalgia nor musculoskeletal pain of any grade were reported in any patients
	Yang et al.[5] (ALTA-3)	Brigatinib	NSCLC (progressed on crizotinib)	Phase 3	125	70	36	11	—
	Yang et al.[5]	Alectinib	NSCLC	Phase 3	122	29	2	2	—
	Camidge et al.[41]	Crizotinib	NSCLC	Phase 3	137	17	1	2	Myalgia was reported in 8% patients. Musculoskeletal pain was reported in 8% patients. No grade 3 or higher myalgia or musculoskeletal pain was reported
	Shi et al.[42]	Iruplinalkib (WX-0593)	NSCLC	Phase 2	146	34.9	—	2.1	—
MEK1/2, B-Raf	Dummer et al.[43]	Binimetinib and encorafenib	Melanoma	Phase 3	192	27.1	7.8[c]	—	—
	Monk et al.[4]	Binimetinib	Ovarian carcinomas	Phase 3	200	50	26	—	—
	Tabernero et al.[a 44]	Encorafenib, binimetinib, and cetuximab	Colorectal cancer	Phase 3	222	34.3	3	—	—

(Continues)

TABLE 3 (Continued)

Primary targets	Reference/Trial name	TKI/drug combination	Tumor type	Trial type	N	All grade (%)[a]	≥ grade 3 (%)[a]	Dose Reduction (%)	Symptoms
	Ascierto et al. [52]	Binimetinib	NRAS mutated melanoma	Phase 2	30	37	23	23	Increase in serum CK level was the most common grade 3–4 TRAEs, though they were mostly asymptomatic. The most frequent symptoms of increased CK concentrations were muscle weakness in 4 patients and myalgia in 2 patients.
	Ascierto et al. [52]	Binimetinib	Val600 BRAF mutated melanoma	Phase 2	41	22	17	12	
	Watanabe et al. [53]	Binimetinib	Solid tumors	Phase 1	21	81	33	—	No clinical symptoms of myopathy were observed
	Bardia et al. [54]	Binimetinib and buparlisib	Solid tumors	Phase 1b	89	59.6	27	—	—
	Ascierto et al. [5]	Cobimetinib and Vemurafenib	Melanomas	Phase 3	247	35	12	—	Increased serum CK level was generally asymptomatic and managed by close clinical observation
	Dummer et al.[43]	Vemurafenib	Melanomas	Phase 3	186	2.2	0	—	—
	Ascierto et al. [5]	Vemurafenib and placebo	Melanomas	Phase 3	247	3	<1	—	—
	Gross et al. [55]	Selumetinib	Neurofibromatosis	Phase 1/2	74	76	9	7	The most common AE were asymptomatic CK. All participants who had a CK ≥ grade 2 (between 2.5 and 5 times above the upper limit of normal) had CK isoenzymes checked at the first occurrence, and no one had a concerning elevation in CK-MB, indicating there was no significant cardiac component to the elevated CK
MEK1/2, PI3K	Bedard et al. [56]	Trametinib and buparlisib	RAS- or BRAF-mutant non–small cell lung, ovarian, or pancreatic cancer	Phase 1b	113	45.1	14.2	—	—

TABLE 3 (Continued)

Primary targets	Reference/Trial name	TKI/drug combination	Tumor type	Trial type	N	All grade (%)[a]	≥ grade 3 (%)[a]	Dose Reduction (%)	Symptoms
B-Raf	Tabernero et al.[44]	Encorafenib and cetuximab	Colorectal cancer	Phase 3	216	3.7	0	—	—
	Tabernero et al.[44]	Either cetuximab and irinotecan or cetuximab and FOLFIRI	Colorectal cancer	Phase 3	193	7.3	0.5	—	—
BCR-Abl	Adenis et al.[50]	Imatinib	GIST	Prospective	87	45	0	—	—
	Gordon et al.[16]	Imatinib	CML/GIST	Prospective	25	80	8	—	Of CK elevations patient, 3 had other medical conditions that could have contributed. 1 patient had a family history of myopathy, and 2 patients had a history of hypothyroidism although they were euthyroid during the study period. 1 patient had alcohol use of approximately 2 drinks nightly, and seven patients were on other medications associated with CK elevations (statins, antidepressants, and/or antipsychotics)
	Gambacorti-Passerini et al.[51] CTCAE 3.0	Imatinib	CML	Phase 3	251	20	5	—	—
	Bankar et al.[52] CTCAE 5.0	Imatinib	CML	Retrospective	221	76	—	—	Three patients experienced rhabdomyolysis while on treatment with imatinib and had to discontinue the treatment.

(Continues)

TABLE 3 (Continued)

Primary targets	Reference/Trial name	TKI/drug combination	Tumor type	Trial type	N	All grade (%)[a]	≥ grade 3 (%)[a]	Dose Reduction (%)	Symptoms
	Franceschino et al.[53]	Imatinib	CML	Retrospective	50	56[d]	—	—	In a few cases (4%), treatment was interrupted as a precaution because of high (>1000) CK. No clinical signs of myopathy were noted and CK values returned within the normal range after imatinib discontinuation. Once imatinib was restarted, CK values tended to rise again. Myocardial-CK (CK-MB) values were evaluated in 6 patients with a large increase in total CK levels (>800) and found to be normal
	Bankar et al.[52]	Dasatinib	CML	Retrospective	31	65	—	—	—
	Bankar et al.[52]	Bosutinib	CML	Retrospective	8	50	—	—	—
	Réa et al.[54]	Asciminib	CML	Phase 3	156	25	1.9	—	—
	Réa et al.[54]	Bosutinib	CML	Phase 3	76	23.7	5.3	—	—
	Gambacorti-Passerini et al.[51]	Bosutinib	CML	Phase 3	248	8	1	—	—
	Bankar et al.[52]	Nilotinib	CML	Retrospective	23	43	—	—	—
Flt3	Perl et al.[55]	Gilteritinib	AML	Phase 3	246	13.4	5.3	—	—
	Usuki et al.[56]	Gilteritinib	AML	Phase 1	24	37.5	12.5	—	—
EGFR	Lu et al.[57]	Aumolertinib	NSCLC	Phase 3	214	35.5	7	2.8	No patient had a CK increase associated with rhabdomyolysis, and CK increase did not manifest as a serious event
	Malik et al.[58]	Osimertinib	NSCLC	Phase 4	60	10	—	3.3	—
	Parafianowicz et al.[10]	Osimertinib	NSCLC	Case series	38	10	3	—	4 patients developed myositis
	Xiong et al.[59]	Oritinib	NSCLC	Phase 2	286	28	4.5	—	—
	Wang et al.[60]	Sunvozertinib	NSCLC	Phase 2	104	57.7	17.3	—	—
VEGFR, RET	Motzer et al.[61]	Sunitinib	RCC	Phase 3	375	49	3	—	—
	Adenis et al.[50]	Sunitinib	Solid	Perspective	155	29	—	—	—

TABLE 3 (Continued)

Primary targets	Reference/Trial name	TKI/drug combination	Tumor type	Trial type	N	All grade (%)[a]	≥ grade 3 (%)[a]	Dose Reduction (%)	Symptoms
RET, VEGFR2	Yamanaka et al.[62]	Cabozantinib	RCC	Retrospective	13	61.5	—	—	2 patients with grade 2 or 3 of CK elevation developed rhabdomyolysis with muscle weakness and/or acute kidney injury
	Okubo et al.[63]	Cabozantinib	HCC	Prospective	14	21	0	—	The patients were without myalgia or muscle cramp
VEGFR1/2/3	Adenis et al.[50]	Sorafenib	solid	Perspective	155	19	—	—	—
FGFR2	Goyal et al.[64]	Futibatinib	Cholangiocarcinoma	Phase 2	103	10	3	—	—
PDGFRα	Li et al.[65]	Avapritinib	GIST	Phase 1/2	65	46	—	8	None of the events resulted in significant clinical symptoms
c-MET	Saleh et al.[66]	Merestinib and ramucirumab	Colorectal cancer	Phase 1	23	13	4.3	—	—
RET	Schoffski et al.[67]	BOS172738	NSCLC and medullary thyroid cancers	Phase 1	67	54	—	—	—

Note: Blank entries: not mentioned.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BID, twice daily; BIN, binimetinib; CML, chronic myeloid leukemia; ENC, encorafenib; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HLH, hemophagocytic lymphohistiocytosis; IBM: inclusion body myositis; NSCLC, non-small cell lung cancer; PEM, pembrolizumab; QD, once daily; RCC, renal cell carcinomas; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.

[a]Grade 1: CK 1–2.5 ULN, Grade 2: 2.5–5 ULN, Grade 3: 5–10 ULN, and Grade 4: >10 ULN; Grade designation as per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3/4/4.03/5.

[b]The initial protocol mandated dose interruption or reduction of brigatinib in the presence of grade 3 or 4 blood creatine phosphokinase level (CPK) elevations, irrespective of associated symptoms. In February 2021, the protocol was revised to require accompanying symptoms (grade 2 muscle pain or weakness) for dose modifications in cases of grade 3 or 4 CPK elevation.

[c]In patients with BRAF mutation-positive melanoma receiving binimetinib with encorafenib, rhabdomyolysis was reported in 1 patient (0.1%).

[d]Elevated CK was defined as grade 2 or higher, showing higher than 620 U/L in men or 383 U/L in women during dasatinib treatment.

was reported in 50/155 patients (32%). CK elevation was observed in 54 patients (35%). The incidence rates of CK elevation among patients treated with imatinib, sunitinib, sorafenib, HER1/2 antagonists, and other TKIs were found to be 45%, 29%, 19%, 14%, and 20%, respectively. Notably, patients who received any TKI treatment for more than 6 months demonstrated an increased likelihood of elevated CK levels. CK elevation occurred in 45% of 87 patients treated with imatinib in this study, while Franceschino et al.[53] reported a similar occurrence of CK elevation in 50 patients with CML receiving imatinib treatment. Considering that the patients included in Adenis's study had incomplete medication data at baseline and many experienced complications associated with concomitant medication usage, it is plausible that elevated CK levels could be attributed to their underlying medical conditions or other medications.[53]

An updated analysis of the phase III BELA trial (NCT00574873) evaluated the safety profile and toxicity management of bosutinib compared with imatinib in adults with newly diagnosed chronic phase CML after more than 30 months from accrual completion. Among the 248 patients in the bosutinib group and 251 patients in the imatinib group who received at least one dose of treatment, there was a significantly lower incidence of CK elevation observed with bosutinib compared with imatinib (8% vs. 20%, $p < 0.001$).[51] When comparing the kinase inhibition profile of imatinib versus bosutinib, in addition to bcr-abl TK inhibition, imatinib is also an inhibitor of the receptor TKs of platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit. PDGF and its receptor (PDGFR) are integral to the pathophysiology of fiber regeneration, fibrosis, and the progression of muscle dystrophy, inhibition of which may potentially lead to direct myotoxic effects. In contrast, bosutinib does not inhibit c-kit or PDGFR but predominantly targets the apoptosis-linked STE20 kinases. This distinct kinase inhibition profile may contribute to the higher incidence of CK elevation by imatinib than bosutinib.[75]

A phase III, open-label, randomized study of asciminib, a BCR-ABL1 inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP), versus bosutinib in CML after two or more prior TKIs, the major molecular response (MMR) rate at week 24 was 25.5% with asciminib and 13.2% with bosutinib.[54] CK elevation was found in 25% in asciminib group and 23.7% in bosutinib group.[54] Gilteritinib is an oral, potent, selective FLT3 inhibitor with single-agent activity in relapsed or refractory FLT3-mutated AML; of the 246 patients in phase III study of gilteritinib, 13.4% of patients had increased CK, and 5.3% were Grade 3–5 including serious, life-threatening, and fatal adverse reactions.[55]

EGFR inhibitors (osimertinib, aumolertinib, oritinib, and sunvozertinib)

The incidence of serum CK elevation induced by EGFR-TKIs (osimertinib, aumolertinib, oritinib, and sunvozertinib) is 10%,[10,58] 35.5%,[57] 28%,[59] and 57.7%,[60] respectively. The third-generation EGFR-TKIs osimertinib, aumolertinib, and oritinib are oral and irreversible third-generation EGFR-TKIs selectively targeting both sensitizing EGFR and EGFR T790M mutations.[59,76,77] In AENEAS phase III study (NCT03849768), the most common AEs in the aumolertinib group was CK increase with 35% of all grade and 7% ≥Grade 3.[57] In the four major clinical studies of osimertinib: AURA (NCT01802632),[78] AURA2 (NCT02094261),[53] AURA3 (NCT02151981),[79] and FLAURA (NCT02296125),[80] CK elevation was only reported in AURA2, none of which explicitly reported the occurrence of adverse effects such as myositis, myalgia, or rhabdomyolysis. But fatigue, weakness, and elevated liver enzymes may be manifestations of muscle damage and cause CK elevation as reported in the above study. In a study conducted in India assessing the safety of osimertinib in patients with stage IV NSCLC with EGFR T790M mutation-positive, CK increase (10%) was one of the most frequently observed treatment-emergent adverse events (TEAEs). Parafianowicz et al.[81] reported that myositis accompanied by elevated CK occurred in 4 out of 38 patients receiving osimertinib (10%).

A phase II study assessing SH-1028 (oritinib) in EGFR T790M-positive advanced NSCLC showed that the incidence of treatment-related CK elevation was 28% ($n = 286$), and the incidence of CK elevation ≥Grade 3 was 4.5%.[59] Sunvozertinib (DZD9008) is a selective, irreversible EGFR exon20 insertion inhibitor. In phase II WU-KONG6 study, 104 patients received 300 mg sunvozertinib, 57.7% experienced CK elevation, and 17.3% were ≥Grade 3.[60]

FGFR2, VEGFR, RET, FKBP12/mTOR, VEGFR2 inhibitors (futibatinib, lenvatinib, sunitinib, everolimus, and cabozantinib)

The incidence of CK elevation induced by sunitinib, cabozantinib, futibatinib is 29%–49%,[50,61] 21%–61.5%,[62,63] and 10%,[64] respectively. A randomized phase III trial (NCT00083889) demonstrated superiority of sunitinib over interferon alfa in PFS as first-line treatment for metastatic renal cell carcinoma (RCC), based on CTCAE 3.0, 49% of patients in sunitinib group displayed CK elevation.[61]

A retrospective study of 13 patients with advanced RCC who were treated with cabozantinib monotherapy. Eight (61.5%) experienced an increase in serum CK levels, with five patients classified as Grade 1 elevation. The elevation

of CK occurred at a median of 14 days after the initiation of cabozantinib treatment. Rhabdomyolysis, accompanied by muscle weakness and/or acute kidney injury, developed in two patients who experienced Grade 2 or 3 CK elevation.[62] In TAS-120-101 study (NCT02052778), futibatinib (a fibroblast growth factor receptor (FGFR) 1–4 inhibitor) was investigated in FGFR2 fusion-positive or FGFR2 rearrangement-positive intrahepatic cholangiocarcinoma. Ten percent of the patients exhibited serum CK elevation, among whom 3% were considered ≥Grade 3.[64]

KIT, PDGFRα, c-MET, and RET inhibitors (ripretinib, avapritinib, BOS172738, and merestinib)

The incidence of CK elevation induced by ripretinib, avapritinib, BOS172738, and merestinib plus ramucirumab combination was 21%, 46%,[65] 54%,[67] and 13%,[66] respectively. Avapritinib is a type 1 kinase inhibitor designed to potently and selectively inhibit oncogenic KIT/PDGFRA mutants by targeting the kinase active conformation. A phase I/II bridging study (NCT04254939) evaluating the safety and the antineoplastic activity of avapritinib in Chinese patients with unresectable/metastatic GISTs ($N=65$); 30 patients had elevated CK (46%), and five patients were ≥Grade 3 (8%).[65] In a phase Ia/b study (NCT02745769), patients were treated with combination of the type II MET kinase inhibitor, merestinib, and the antivascular endothelial growth factor receptor 2 monoclonal antibody, ramucirumab; CK elevation was occurred in 13% of patients.[66] BOS172738 is a selective oral RET kinase inhibitor designed with nanomolar potency against RET and >300-fold selectivity against vascular endothelial growth factor receptor 2, in phase I study (NCT03780517); 54% of patients had CK elevation among 67 patients with RET-altered advanced solid tumors.[67]

Clinical symptoms / adverse events associated with TKI-induced CK elevation

Myopathy, myalgia, weakness, and IBM

The most common symptom associated with serum CK elevation is myopathy. A myopathy is a disorder characterized by a primary functional or structural impairment of the skeletal muscles. Myopathy is presented with (1) Proximal symmetric weakness, which may manifest acutely, subacutely, or chronically. (2) Muscle bulk that is reduced, preserved, or enlarged. (3) Muscle pain or discomfort upon palpation (myalgia). (4) Muscle stiffness or cramps. (5) Asthenia (weakness) and fatigue. (6) Myoglobinuria (the presence of myoglobin in the urine).[81] In a phase II study (NCT01320085), patients with NRAS-mutated or BRAF-mutated advanced melanoma receiving at least one dose of binimetinib ($n=71$) were investigated. Twenty patients displayed CK elevation (28.2%) and their most common symptoms were muscle weakness (4 out of 20 patients) and myalgia (2 out of 20 patients).[73] Patients with myopathy are more likely to develop elevated CK. Adenis et al. investigated serum CK increase in 155 solid tumor patients treated with TKI. The presence of spontaneous myalgias was significantly associated with abnormal CK levels (26/50, 52% in case of myalgias vs. 28/105, 27% in the absence of myalgias, chi-squared test: $p=0.002$).[50]

There are notable case reports of myopathy accompanied by significant CK elevation induced by osimertinib, alectinib, and dasatinib, specific TKI targeting EGFR, ALK, and BCR/ABL, respectively. In a few clinical studies, NSCLC patients treated with osimertinib developed severe leg spasms, myalgia, or myositis, which were associated with a significant elevation of serum CK level from 989 U/L to 29,680 U/L.[7,9,82] A patient with ALK-rearranged lung cancer treated with alectinib after a temporary drug halt due to elevated CK levels of 2673 U/L; the treatment was successfully resumed without further myositis episodes.[83] Moreover, a 69-year-old man with imatinib-refractory CML developed progressive muscle weakness and IBM following treatment with dasatinib, which was characterized by a significant rise in serum CK levels (>Grade 3).[11] Due to the promising dasatinib-induced tumor remission in this patient, dasatinib therapy was resumed under close clinical monitoring.

Cardiotoxicity

TKI-induced serum CK elevation is generally related to skeletal muscle damage. In the case of TKI-cardiotoxicity, the related rise of serum CK (particularly, the CK-MB isotype preferentially expressed in the heart) may be utilized as a potential biomarker for monitoring. Electrocardiogram (ECG) screening is recommended for patients at risk for a thorough evaluation of their cardiovascular condition prior to initiating TKI therapy, in order to mitigate the potential cardiotoxic effects such as arrhythmias, acute coronary syndrome (ACS), congestive heart failure, and pleural effusion.[84] Interestingly, Al-Ali et al.[85] investigated 113 patients treated with imatinib for at least 6 months. CK electrophoresis revealed elevated CK-MM in 83% (including one patient with Makro-CK-I) and elevated CK-MB in 17%. Therefore, identifying the specific subtype of elevated CK may be critical in determining the presence of myocardial damage following TKI treatment.

Pechbach et al. reported an asymptomatic and reversible ventricular arrhythmia induced by dasatinib in a 54-year-old patient on second-line treatment for the management of chronic phase CML. Dasatinib was temporarily discontinued for 1 week to ensure complete systemic elimination and then restarted and associated with an anti-arrhythmic regimen of metoprolol and flecainide. The patient developed proximal limb myalgias following the initial dose. A 24-h ECG was repeated, revealing a restoration to normal sinus rhythm. The patient experienced a good clinical and paraclinical response following homograft.[12] The combination of TKI and immune checkpoint inhibitors may be associated with more toxicities. Guo et al. reported two cases having myocarditis due to cobimetinib and atezolizumab treatment both received long-term pembrolizumab before disease progression. One patient with CK elevated to 1165 U/L and high-sensitivity troponin T (hs-TnT) at 77 ng/L. Transthoracic echocardiography (TTE) revealed a left ventricular ejection fraction (LVEF) of 55%. Cardiac magnetic resonance imaging (CMRI) demonstrated midwall myocardial edema and late gadolinium enhancement (LGE) in the basal, anterolateral, mid-inferior, and inferior segments consistent with myocardial inflammation and necrosis. The other patient was asymptomatic but had an elevated CK level of 630 U/L and hs-TnT level of 455 ng/L. Both patients received methylprednisolone and corticosteroids which resulted in decreased levels of CK and hs-TnT, respectively. However, one patient experienced disease progression 4.6 months after the diagnosis of myocarditis, while the other patient did not respond to alternative ipilimumab-plus-nivolumab therapy and complications related to immune-related nephritis requiring prednisolone.[13]

Rhabdomyolysis

Rhabdomyolysis is characterized by progressive proximal muscle weakness, general weakness, and muscle pain, especially in the lower extremities, and brown-colored urine.[86] In laboratory work-up, clinicians commonly use serum CK levels that exceed five times the ULN value to diagnose rhabdomyolysis.[86] Severe symptomatic rhabdomyolysis is a rare AE reported in a few pivotal clinical studies investigating TKIs. However, monotherapy of a number of TKIs (including cabozantinib, cobimetinib, erlotinib, dasatinib, trametinib, imatinib, sunitinib, sorafenib, and osimertinib), combination therapy of binimetinib with encorafenib, dabrafenib and trametinib, ribociclib and simvastatin, pazopanib and rosuvastatin, ribociclib and statin, and triplet therapy of palbociclib, fulvestrant, and statin (atorvastatin), palbociclib, fulvestrant, and statin (simvastatin) have been reported to induce rhabdomyolysis. The severity of CK elevation varied widely among patients, from >5 times upper normal limit (UNL) to levels exceeding 10 times UNL, encompassing a range from reversible symptoms to life-threatening cases of rhabdomyolysis. In the coBRIM trial (NCT01689519), Grade 3 or 4 CK elevations, including asymptomatic elevations over baseline, occurred in 12% of patients receiving cobimetinib with vemurafenib and 0.4% of patients receiving vemurafenib. The median time to first occurrence of Grade 3 or 4 CK elevations was 16 days in patients receiving cobimetinib with vemurafenib; the median time to complete resolution was 15 days. Elevation of serum CK increase of more than 10 times the baseline value with a concurrent increase in serum creatinine of 1.5 times or greater compared with baseline occurred in 3.6% of patients receiving cobimetinib with vemurafenib and in 0.4% of patients receiving vemurafenib.[6] In the COLUMBUS trial (NCT01909453), rhabdomyolysis was reported following combination therapy with binimetinib and encorafenib. Elevation of serum CK was also reported in 58% of patients treated with binimetinib-encorafenib combination. In patients with BRAF mutation-positive melanoma receiving binimetinib plus encorafenib ($n = 690$), rhabdomyolysis was reported in one patient (0.1%).[87]

Two patients showed a more than 50% reduction in left ventricular ejection fraction and massive elevation of CK, which was accompanied by myoglobinuria and renal failure.[60] These two cases may be particularly severe because both patients were nephrectomized and their conditions were complicated by multiorgan failure. A retrospective study of 13 advanced RCC patients treated with cabozantinib monotherapy. Eight patients (61.5%) experienced an increase in serum CK levels, among which two patients with Grade 2 or 3 CK elevation developed rhabdomyolysis characterized by muscle weakness and/or acute kidney injury.[62]

There were a few clinical reports about the potential risk of rhabdomyolysis resulting from drug–drug interactions between TKIs and statins. It has been reported that patients with RCC and advanced breast cancer could experience severe muscle toxicity following pazopanib, ribociclib, or palbociclib therapy if the patients were also on statins (such as rosuvastatin, simvastatin, and atorvastatin).[20–22,26,88] Statins, while effective at lowering cholesterol, have a rare but serious side effect of muscle injury, which can escalate to rhabdomyolysis and potentially leading to kidney damage. The interaction is exacerbated by the inhibition of CYP3A4, an enzyme responsible for metabolizing some certain statins like simvastatin, rosuvastatin, and atorvastatin, by some TKIs (e.g., palbociclib and ribociclib) and a potential inhibitor of the uptake transporter OATP1B1 of statin.[26] The reports highlighted cases with CK levels ranging from 3070 to 37,000 U/L and

even a fatal outcome with levels at 14,572 U/L.[20–22,26,88] Serious symptoms associated with rhabdomyolysis caused by statins and TKIs include secondary acute kidney injury,[21] tetraparesis,[26] and necrotizing rhabdomyolysis related to death.[22] These interactions suggest that clinicians should be vigilant in monitoring CK levels when prescribing combinations of these medications. The genetic predisposition of the patients should also be considered, which could affect drug metabolism.

Other symptoms or adverse events

Elevated serum CK levels were also associated with skin rash induced by antineoplastic drugs. Garcia et al.[89] investigated the levels of CK in 287 patients on TKI therapy (targeting EGFR/HER2, m-TOR, VEGFR, SRC/ABL, Aurora kinase, BRAF/MEK, PARP, CDK, or A5B1 integrin). Patients with Grade 2/3 rash were found to display the highest incidence of serum CK elevation (67%) compared with those with no or Grade 1 rash. Following resolution of the rash, a significant decrease in CK values was observed in 25 systematically monitored patients (8.7%) ($p = 0.012$). In vitro exposure of human keratinocytes (HaCaT) to EGFR, MEK, and PI3 kinase/m-TOR inhibitors resulted in upregulated expression of CK-B but not CK-M or mitochondrial-CK.[89] Binimetinib treatment in two melanoma patients was reported to trigger varying AEs accompanied by serum CK elevation. One patient experienced severe myalgia, Grade 3 CK elevation, Grade 2 acneiform dermatitis, bilateral retinopathy, and increased eye pressure. The other patient suffered from Grade 4 CK elevation and Grade 2 facial acneiform dermatitis without myalgia.[18]

Management of adverse effect associated with CK elevation after TKI therapy

A representative algorithm for dose adjustment following CK elevation has been proposed based on the clinically approved United States prescribing recommendation of various TKIs. Appropriate dose adjustment is recommended according to the severity of serum CK elevation (Grade 1: CK 1–2.5 times ULN; Grade 2: 2.5–5 times ULN; Grade 3: 5–10 times ULN; and Grade 4 > 10 times ULN) (Table 4). Briefly, if CK elevation is considered Grade 0–2, there is no need to interrupt the treatment or adjust the dose. For some TKIs (brigatinib, binimetinib, and gilteritinib), serum CK assessment is recommended prior to treatment. If the extent of CK elevation is higher than or equal to Grade 3, the TKI therapy should be suspended for a period until the situation is improved to Grade 1/2 or baseline. Afterward, the TKI therapy may be resumed in full dose or at a reduced dose. If there is no improvement in serum CK level following the treatment suspension, the TKI therapy should be permanently discontinued.

Table 5 summarized representative clinical cases of serum CK elevation which is accompanied by myopathy, myositis, IBM, ventricular arrhythmia, myocarditis, rhabdomyolysis, acneiform dermatitis, and other TKI-induced symptoms. In most situations, after excluding the possibility of CK elevation caused by other confounding factors (comorbidities and concurrent medications), temporary suspension or dose reduction of TKI was shown to ameliorate the clinical symptoms. Some cases revealed that dose reduction of TKI could resolve the symptoms while still maintaining tumor suppression (Table 5). In NSCLC patients on osimertinib therapy, the clinical symptoms (including myositis) associated with elevated serum CK could be relieved by employing a two consecutive days on and 1 day off regimen, approximately 53 mg/day, which is higher than half dose (40 mg/day).[81] In another case report of NSCLC patient who developed myositis following osimertinib therapy, dose reduction by half after a one-month osimeritinib suspension was found to resolve the symptoms despite the persistent elevation of CK above the normal range.[9] On the contrary, in melanoma patient treated with binimetinib, treatment suspension, and subsequent dose reduction was adopted.[18] Upon resumption of binimetinib therapy, the same AEs recurred, another dose reduction of 2-weeks-on and 1-week-off schedule with reduced dose (30 mg b.i.d.) was commenced. With this dose reduction regimen, CK elevation was maintained between Grade 1 and Grade 3. Importantly, the severe AEs including acneiform dermatitis and retinopathy were mostly resolved and an effective suppression of tumor burden was observed.[18] Intermittent dosing of MEK inhibitors has been proposed as a potential strategy to prevent drug resistance in melanoma. The underlying hypothesis is that the on-treatment periods target drug-sensitive tumor cells, while the off-treatment intervals drive drug-resistant cells into cell cycle arrest and apoptosis. Early treatment with MEK inhibitors shows higher tumor immunogenicity, indicating a strong antitumor immune response. However, prolonged exposure can trigger a phenotypic switch in melanoma cells, leading to increased invasiveness and reduced expression of melanocytic differentiation markers in MITF-expressing cells.[101] There is study reporting a surge of T cells in the first week, followed by a decline, suggesting reduced immunogenicity over time.[102] Choi et al.[103] found that pulsatile treatment better maintains T-cell activity and extends survival in KRAS-mutant cancers. In another case report of melanoma patient experiencing trametinib-induced rhabdomyolysis, a reduced dose of dabrafenib (200 mg/day) and

TABLE 4 Representative algorithm for treatment interruption and dose reduction of tyrosine kinase inhibitor (TKI) therapy as recommended by the approved United States Prescribing Information of various TKIs. Appropriate dose adjustment is recommended according to the severity of serum CK elevation.

Drug	Grade or severity of CK elevation[a]	Grade or severity of muscle symptom[b]	Treatment	Dose adjustment recommendation
All TKI	Grade 0–2	—	Unaltered	No modification
Grade 3 or 4	Grade 2 or higher symptoms	First recurrence: try to restart at full dose Second recurrence: reduce the dose at the next lower dose If recurrence after 60 mg, the drug should be permanently discontinued		
Cobimetinib[90]	Grade 4	—	Suspend therapy for up to 4 weeks	If improved to Grade 3 or lower, resume at the next lower dose level If not improved within 4 weeks, permanently discontinue
	Any grade	Myalgia		
Binimetinib[91]	Grade 4 asymptomatic	—	Suspend therapy for up to 4 weeks	If improved to Grade 0–1 resume at a reduced dose If not resolved within 4 weeks, permanently discontinue
	Any grade	With symptoms or with renal impairment		
Encorafenib[92]	Grade 3	—	Suspend therapy for up to 4 weeks	If improves to Grade 0–1 or to pretreatment/baseline level, resume at reduced dose If no improvement, permanently discontinue
	—	Grade 3		
	Grade 4	—	Suspend therapy for up to 4 weeks or permanently treatment discontinuation	If improves to Grade 0–1 or to pretreatment/baseline level, resume at reduced dose If no improvement, permanent treatment discontinuation is recommended
	—	Grade 4		
Gilteritinib[93]	≥Grade 3	—	Interrupt until toxicity resolves or improves to Grade 1	Resume TKI therapy at 80 mg
	—	≥Grade 3		

[a]Grade 1: CK 1–2.5 times ULN; Grade 2: 2.5–5 times ULN; Grade 3: 5–10 times ULN; and Grade 4: >10 times ULN; Grading is defined according to National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 or 4.03.

[b]Muscle symptoms including muscle pain or weakness.

trametinib (1.5 mg/day) was reported to allow the normalization of serum CK level and resolution of rhabdomyolysis. Upon further follow-up, the patient developed muscle weakness with a slightly elevated serum CK level. A further dose reduction to dabrafenib (150 mg/day) and trametinib (1 mg/day) was recommended, when the patient was still free from rhabdomyolysis. Importantly, both primary and metastatic tumor lesions of the patient were under control even on the reduced doses of dabrafenib and trametinib for at least 6 months.[98]

The intermittent dosing schedules serve several purposes: (1) Mitigating toxicity: By allowing periods for the body to recover, the intermittent approach helps to reduce the severity and duration of AEs; (2) Maintaining efficacy: Despite the reduced dosing frequency, the therapeutic response could be sustained; and (3) Preventing drug resistance: The strategy may also delay the development of drug resistance by inducing a fitness deficit for drug-resistant cells during treatment breaks, enhancing the expression of immunostimulating molecules, and reducing immunosuppressive factors, and maintaining the apoptotic and cell cycle arrest effect.[18]

High-intensity exercise is not recommended to patients on TKI treatment because strenuous exercise could promote serum CK elevation and thereby aggravating related symptoms. Patients with workout routines should monitor their serum CK level periodically when receiving high-dose TKI therapy. They should also be on the watch out for signs and

TABLE 5 Management and follow-up treatments of cancer patients experiencing serum creatine kinase (CK) elevation, who were accompanied by myopathy, myositis, IBM, ventricular arrhythmia, myocarditis, rhabdomyolysis, acneiform dermatitis, and other tyrosine kinase inhibitor (TKI)-induced symptoms.

TKI	Target	Cancer type	Symptom(s)	CK value (U/L)	Management	Resolution of adverse effects after intervention	Follow-up anticancer treatment
Osimeritinib[7]	EGFR	NSCLC	Myopathy	989	Discontinuation	CK level improved but higher than normal	Osimertinib
Gefitinib[8]	EGFR	NSCLC	Myositis	Grade 2	Discontinuation	Muscle symptoms disappeared with CK normalization	—
Osimertinib[9]	EGFR	NSCLC	Myositis	1238	Discontinuation	Myalgia subsided and CK levels decreased	Half-dose osimertinib (40 mg)
Osimertinib[10]	EGFR	NSCLC	Myositis	790	Discontinuation	CK normalization	2 days on and 1 day off
Osimertinib[10]	EGFR	NSCLC	Myositis	2511	Discontinuation	CK normalization	2 days on and 1 day off
Osimertinib[10]	EGFR	NSCLC	Myositis	596	Discontinuation	CK normalization	2 days on and 1 day off
Osimertinib[10]	EGFR	NSCLC	Myositis	298	Discontinuation	CK normalization	2 days on and 1 day off
Osimertinib[82]	EGFR	NSCLC	Myositis, hepatitis, presynaptic muscle fiber damage caused by profound muscle necrosis	29,680	Discontinuation; Symptom management: prednisone (40 mg orally daily), pulse-dose steroids Solu-Medrol 60 mg intravenous (IV) daily and IV immunoglobulin 1 g/kg daily for 2 days, pyridostigmine 2 mg IV	Distal strength recovery, proximal muscle weakness, able to eat a regular diet and did not require supplemental oxygen and transferred to acute rehabilitation	Chemotherapy and stereotactic brain radiation
Alectinib[83]	ALK, RET	Lung cancer with BM	Myositis	2673	Discontinuation	—	Alectinib
Dasatinib[11]	BCR-Abl	CML	IBM	>Grade 3	TKI therapy was not discontinued because of complete molecular remission by dasatinib and the patient did not receive any additional treatment	CK levels remain unchanged, clinical status has not worsened, and he remains with levels of BCR-ABL indicating a minimum of molecular response 4.5	Dasatinib
Dasatinib[12]	BCR-Abl	CML	Ventricular arrhythmia	Elevated CK with myalgias	Suspended for 7 days	Electrocardiogram reading returned to baseline	Dasatinib, metoprolol, and flecainide
Cobimetinib and atezolizumab[13]	MEK1/2	Melanoma	Myocarditis	1165	Methylprednisolone	CK and hs-TnT reduced, preserved LVEF and reduced midwall edema	—
Cobimetinib and atezolizumab[13]	MEK1/2	Melanoma	Myocarditis	377	Methylprednisolone	CK and hs-TnT normalization	Ipilimumab and nivolumab (ineffective)

(Continues)

TABLE 5 (Continued)

TKI	Target	Cancer type	Symptom(s)	CK value (U/L)	Management	Resolution of adverse effects after intervention	Follow-up anticancer treatment
Erlotinib[14]	EGFR	NSCLC	Rhabdomyolysis	Grade 3	Discontinuation; Symptom management: hydration and intravenous bicarbonate infusion	All vital signs returned to the normal ranges, reduction of myalgia	—
Dasatinib[15]	BCR-Abl	Ph + CML	Rhabdomyolysis	3831	Dasatinib was stopped and the patient was given aggressive hydration, allopurinol, and diuretics	—	—
Imatinib[16]	BCR-Abl	CML	Rhabdomyolysis		Discontinuation, intravenous hydration, steroids	Normalization of CK	Dose reduction of imatinib
Imatinib[17]	BCR-Abl	Fibromatosis (desmoid tumors)	Rhabdomyolysis	1068	Discontinuation	Normalization of CK	Radiotherapy
Sunitinib[a,94]	VEGFR2	RCC	Rhabdomyolysis	3849	—	Patient succumbed	—
Sunitinib[a,b,94]	VEGFR2	RCC	Rhabdomyolysis	3160	Hemodialysis	Recovered and all laboratory tests normalized	—
Sorafenib[95]	VEGFR1/2/3	HCC	Rhabdomyolysis	10,911	Discontinuation; Symptom management: intravenous fluids	Myalgia and fatigue resolved	Best supportive care
Osimertinib[96]	EGFR	NSCLC	Rhabdomyolysis, acute renal insufficiency, hyperuricemia, metabolic acidosis, and electrolyte disturbances	1470	Osimertinib discontinuation; Symptom management: alkalinization of urine and rehydration	All symptoms improved	—
Dabrafenib and trametinib[97]	B-Raf, MEK1/2	Melanoma	Hemophagocytic lymphohistiocytosis (HLH), rhabdomyolysis	10 times UNL	Treatment discontinuation with basic supportive care (intravenous rehydration and paracetamol) with no requirement for steroids	The patient's condition rapidly improved and EBV viral load was negative in blood after 3 weeks	Vemurafenib/ cobimetinib combination
Dabrafenib and trametinib[97]	B-Raf, MEK1/2	Melanoma	Hemophagocytic lymphohistiocytosis (HLH), rhabdomyolysis	5 times UNL	Treatment discontinuation with supportive care measures (intravenous rehydration and paracetamol) and oral steroids (1 mg/kg/day)	Condition rapidly improved	Encorafenib/ binimetinib combination (including steroid in the regimen)

TABLE 5 (Continued)

TKI	Target	Cancer type	Symptom(s)	CK value (U/L)	Management	Resolution of adverse effects after intervention	Follow-up anticancer treatment
Trametinib[98]	MEK1/2	Melanoma	Rhabdomyolysis	7312	Treatment discontinuation with intravenous fluids administration	Normalization of CK	Dabrafenib 200 → trametinib (1.5 mg) and dabrafenib (200 mg)
Dabrafenib and trametinib[99]	B-Raf, MEK1/2	Melanoma	Rhabdomyolysis	14,328	i.v. prednisolone 40 mg/day with fluid replacement	CK level (186 IU/L) and myoglobin (45 ng/mL) decreased	Nivolumab (2 mg/kg every 3 weeks)
Dabrafenib and trametinib[100]	B-Raf, MEK1/2	Melanoma	Rhabdomyolysis, renal failure, and visual loss	2218	Discontinuation	Most of the side effects resolved within 3 weeks, but some retinal lesions and the abduction deficit persisted	—
Pazopanib and rosuvastatin[20]	VEGFR1/2/3	RCC	Rhabdomyolysis	5719	Discontinuation of both drugs, fluid resuscitation	A full recovery	—
Ribociclib and statin[21]	CDK4/6	Breast cancer	Rhabdomyolysis with secondary AKI	3070	Discontinuation of simvastatin and ribociclib	Condition gradually improved, creatinine gradually decreased to 1.3 mg/dL, GFR to 40.2 mL/min/1.73 m^2	Ribociclib 200 mg, simvastatin was permanently discontinued
Palbociclib, fulvestrant, and statin (atorvastatin)[22]	CDK4/6	Breast cancer	Necrotizing rhabdomyolysis	14,572	Atorvastatin, palbociclib, and fulvestrant were discontinued, hydration, methylprednisolone	Adverse effects continued to deteriorate; patient succumbed	—
Palbociclib, fulvestrant, and statin (simvastatin)[26]	CDK4/6	Breast cancer	Tetraparesis and rhabdomyolysis	>22,000	Atorvastatin, palbociclib, and fulvestrant were discontinued, hydrated with 4 L saline i.v., intravenous immunoglobulin (IVIG) 0,4 g/kg	Gait function restored after 2 weeks of hospitalization and no signs of neuromuscular deficiency after 1-year follow-up	—
Ribociclib and simvastatin[88]	CDK4/6	Breast cancer	Rhabdomyolysis	CK: 37,000 U/L, creatinine: 105 µmol/L Grade 3 neutropenia AST/ALT: 1314/377 UI/L	Discontinuation of ribociclib and simvastatin, rehydration was initiated with 2 L of NaCl 0.9% and 1 L of bicarbonate, ICU, intensified hydration with 2 L of NaCl 0.9% for the first 5 h in association with 3 L of glucose 5% on 24 h, intravenous nicardipine	Normalization of blood tests: CK: 102 U/L, creatinine: 63 mmol/L, AST/ALT: 36/77 UI/L	Ribociclib 200 → 400 → 600 mg/day, with good tolerance, and continued 600 mg/day for 3 weeks followed by 7 day off Simvastatin was stopped

(Continues)

TABLE 5 (Continued)

TKI	Target	Cancer type	Symptom(s)	CK value (U/L)	Management	Resolution of adverse effects after intervention	Follow-up anticancer treatment
Binimetinib[18]	MEK1/2	Melanoma	Acneiform dermatitis G2, bilateral retinopathy G1, and eye pressure elevation G2.	Grade 3	Discontinuation	All AEs resolved	Dose reduction of binimetinib (30 mg b.i.d.) and intermittent treatment (3 weeks on and 10 days off)
Binimetinib[18]	MEK1/2	Melanoma	Facial acneiform dermatitis G2 and retinopathy G1, but no myalgias	Grade 4	2-week-on and 1-week-off schedule with reduced dose (30 mg b.i.d.)	CK elevation was between G1 and G3, acneiform dermatitis between G1 and G2, and the retinopathy between G0 and G1	2-weeks-on and 1-week-off schedule with reduced dose (30 mg b.i.d.)

Abbreviations: AKI, acute kidney injury; BM, brain metastases; GFR, glomerular filtration rate; ICU, intensive care unit.

[a]The severity and the outcome may be related both to the multiorgan failure and to the fact that both patients were nephrectomized.

[b]The patient was diagnosed with asymptomatic hypothyroidism during treatment.

symptoms of rhabdomyolysis, such as unexplained pain, tenderness, weakness, or persistent muscle pain.[41]

Factors that influence the pharmacokinetics of TKIs and risk for TKI-associated CK elevation including high-dose TKI therapy, polypharmacy and drug–drug interactions. To alleviate high incidence of CK elevation of brigatinib, the phase III first-line trial introduced brigatinib at a lower dose before dose escalation.[41] Simultaneous use of TKI and statin may induce rhabdomyolysis, especially after long-period treatment of statin. TKIs inhibiting CYP450 isoenzymes, OATP 1B1, or P-gp, may affect the metabolism and tissue distribution of statins, and increase their circulating levels and the risk for statin-associated CK elevation. Treatments can be continued with reduced dose of combination therapy or permanently discontinuation of the suspected statin. It is desirable to assess the benefits of maintaining statin therapy against the potential risk of rhabdomyolysis, cardiovascular events, or other severe symptoms.[22]

Mechanism of TKI-induced serum CK elevation by TKIs in cancer patients

The exact mechanism of TKI-induced CK elevation is not fully understood and may vary depending on specific TKIs. Several potential mechanisms have been proposed as follows.

Direct myotoxic effect

TKIs are known to elicit a direct toxic effect on muscle cells (myocytes), leading to cell damage and death. This myotoxicity can result in the release of intracellular contents, including CK, into the bloodstream.[95] Platelet-derived growth factor (PDGF) and its receptor (PDGFR) are involved in the pathophysiology of fiber regeneration, fibrosis, and progression of dystrophy in muscles. For a few specific TKIs, it was reported that PDGFR and c-abl are inhibited by imatinib mesylate, thereby leading to CK elevation.[15] A significant weight loss has been described in patients taking sorafenib, which was associated with a significant reduction in skeletal muscle mass. Although the mechanism of this muscle loss is unclear, it has been suggested that kinases may play a relevant role in the regulation of muscle protein synthesis.[104] Dasatinib may inhibit the activities of some receptor TKs, including PDGFR.[105]

Mitochondrial dysfunction

Some TKIs can interfere with mitochondrial function in muscle cells (Figure 2).[106] For example, osimertinib has

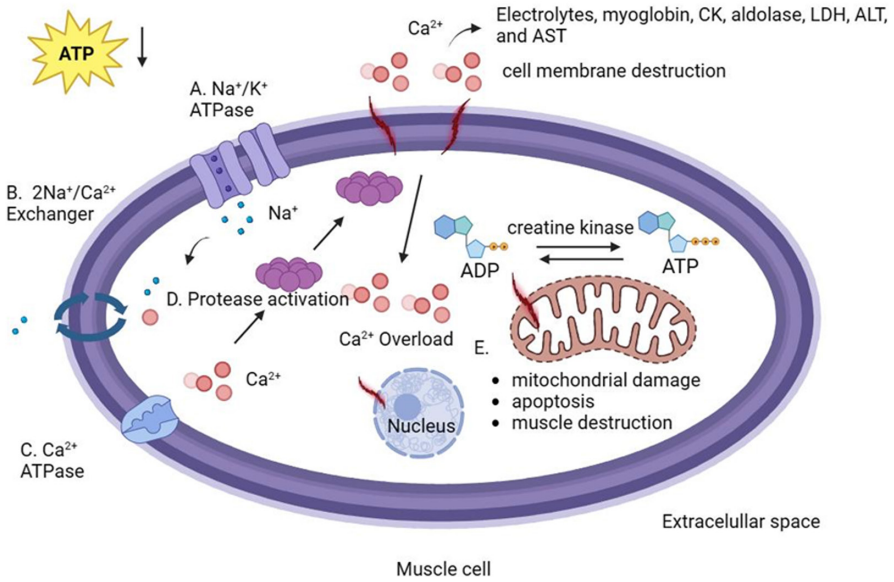

FIGURE 2 Underlying mechanisms leading to rhabdomyolysis and serum CK level elevation. (A) Depletion of energy (ATP) which inhibits the function of Na^+/K^+ ATPase, leading to an increase in intracellular sodium. (B) Increase in intracellular calcium due to the $2Na^+/Ca2^+$ exchanger. (C) Energy depletion also prevents $Ca2^+$ ATPase from pumping out excess calcium, resulting in its accumulation within cells. (D) The buildup of intracellular content of calcium activates proteases (e.g., phospholipase 2 (PLA2)), which break down structural components of cell membranes to facilitate calcium influx. (E) Ultimately, this overload disrupts mitochondrial integrity and triggers apoptosis that leads to muscle cell necrosis.[88]

the potential to induce mitochondrial dysfunction by influencing the levels of adenosine triphosphate (ATP) and disrupting the activities of the ATP synthase (complex V), leading to a decrease in ATP production.[106] Exposure of cardiomyocyte cultures to sorafenib treatment resulted in an increase in PTX3 expression and triggered cytoskeletal remodeling, diminished contractile capacity, suppression of sodium current, and dysfunction of mitochondrial respiration.[107] Mitochondria are responsible for producing energy in cells, and their dysfunction can lead to cell damage and death, thereby releasing CK.

Off-target kinase inhibition

While TKIs are designed to target specific TKs, they may also inhibit other kinases unintentionally. This off-target effect can disrupt various cellular processes, including those in muscle cells, leading to increased serum CK levels.[108]

Electrolyte disturbances

TKIs can cause imbalances in serum levels of electrolytes (such as potassium, calcium, and phosphate),[109] which are essential for muscle function. Electrolyte imbalances can lead to muscle weakness or damage, which can increase CK levels.

Immune-mediated mechanisms

The TKI or the damaged muscle tissue may interact with the body immune system to give rise to an inflammatory response, which could further damage muscle cells and elevate CK levels.[110] Afatinib, sorafenib, and ponatinib activate endoplasmic reticulum stress, which leads to cardiotoxicity by promoting the expression of pro-inflammatory factors and cardiac fetal genes, such as Nfkb1, Il-6, Tnf, Txnip, and Il1b, through the coordinated activation of the PERK and IRE1α signaling pathways.[111]

Ischemia

By affecting blood vessels or blood flow, some TKIs could reduce blood supply (ischemia) to muscles,[112] thereby causing muscle cell damage due to lack of oxygen and nutrients and subsequent CK release. For example, ponatinib and nilotinib have been associated with an increased risk of myocardial ischemia or infarction.[113] Furthermore, crizotinib has been shown to impair the autophagy process, leading to cardiomyocyte death and cardiac injury through the inhibition of MET protein degradation. Reduced autophagy activity has been observed in various cardiac diseases, including ischemia–reperfusion injury, myocardial infarction, cardiac hypertrophy, and heart failure.[114]

Drug–drug interactions

The concomitant consumption of TKIs and other drugs could potentiate muscle damage, thereby leading to higher serum CK levels. Several TKIs (e.g., palbociclib) are known to inhibit CYP450 isoenzymes and drug transporters (including OATP 1B1 and P-gp) (Figure 3), thus increasing the plasma level of statins and the risk for statin-associated CK elevation. Indeed, the combination of palbociclib and simvastatin has been reported to induce severe rhabdomyolysis.[26] Palbociclib is a weak CYP3A4 inhibitor. In clinical drug–drug interaction studies, palbociclib at 125 mg daily increased the mean C_{max} of midazolam (CYP3A4 substrate) by 37% and AUC values by 61% compared with midazolam alone.[115] Similarly, pharmacokinetics studies have shown that co-administration of midazolam with multiple doses of ribociclib increases the midazolam plasma concentration by 280%, compared with the administration of midazolam alone.[116] Therefore, the addition of palbociclib/ribociclib may have significantly increased atorvastatin/simvastatin plasma concentration via CYP3A4-mediated inhibition resulting in statin-induced rhabdomyolysis.[22]

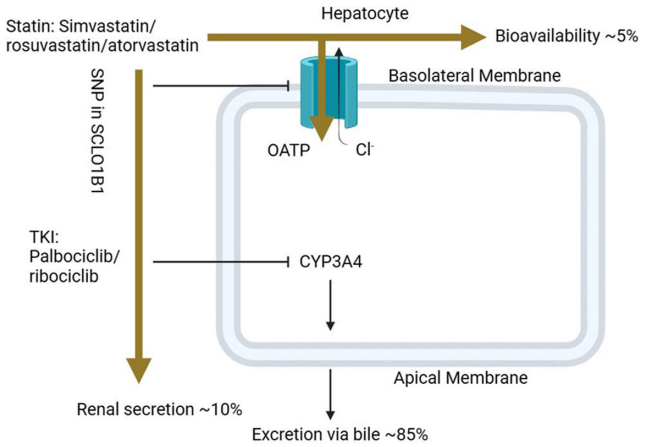

FIGURE 3 Schematic diagram showing the effect of TKIs (e.g., palbociclib and ribociclib) on uptake of statins into hepatocytes. The uptake of statin (simvastatin) into liver cells is regulated by the organic-anion-transporting polypeptide (OATP) transporter. Inside the hepatocytes, statin is metabolized by the liver enzyme CYP3A4. The biotransformed statin is then pumped out of the cells by the ATP-dependent membrane efflux transporters (ABCB1 and ABCG2). Around 85% of statin is cleared from the body through hepatic excretion via hepatocytes and bile, while approximately 10% is eliminated through renal clearance. The remaining 5% represents the bioavailable and active form of the drug in blood circulation. A specific genetic variant rs4149056 in the *SLCO1B1* gene is known to remarkably reduce the transport activity of the OATP transporter. Therefore, patients harboring the *SLCO1B1* SNP rs4149056 are expected to exhibit reduced hepatic uptake of statin and thus leading to an increased statin bioavailability. On the contrary, TKIs could also inhibit the CYP3A4 enzyme to reduce the extent of statin metabolism.[26]

Genetic predisposition

Certain genetic polymorphisms may predispose some patients TKI-mediated muscle damage. The single nucleotide polymorphism (rs4149056) of the hepatic uptake transporter OATP1B1 was associated with a higher chance of progressive rhabdomyolysis in patients receiving palbociclib and simvastatin simultaneously.[26] These mechanisms are not mutually exclusive, and a combination of them may be responsible for the increase in serum CK levels in patients taking TKIs. Further research is necessary to understand the full spectrum of effects that TKIs have on muscle tissue and the mechanisms leading to serum CK elevation.

CONCLUSION AND FUTURE PERSPECTIVES

The elevation of serum CK levels in cancer patients on TKI therapy is a notable clinical manifestation that could hinder the anticancer efficacy. This review provided a latest update about potential mechanisms underlying TKI-induced CK elevation, its clinical implications, and the utility of monitoring serum CK levels for predicting adverse effects.

The physiological function of CK is vital for cellular energy metabolism, muscle contraction, and ATP regeneration. CK is distributed widely throughout the human body, with different subtypes found in various tissues. The elevation of serum CK levels in individual subject can be attributed to multiple factors, including age, gender, race, geographical location, and exercise. Pathological conditions affecting muscle tissues, such as neuromuscular disorders and cardiovascular diseases, and certain medications, including statins, antipsychotics, and antivirals, can also contribute to elevated CK levels.

Molecular targeted TKIs have been found to induce CK elevation in over 20% of cancer patients. It is noteworthy that CK elevation is not preferentially induced by any specific classes of TKIs. The clinical implications of TKI-induced CK elevation are significant. Although under certain circumstance, mostly asymptomatic, elevated CK levels may also manifest as more severe symptoms such as myopathy, myositis, cardiotoxicity, rhabdomyolysis, rash, and acneiform dermatitis. The occurrence of these symptoms may necessitate dose reduction of TKI treatment and therefore hindering antitumor efficacy.

The underlying mechanisms driving TKI-induced serum CK elevation are not fully understood. Numerous

factors contribute to this phenomenon. CK is an essential enzyme involved in cellular energy metabolism and muscle function. TKIs may disrupt the delicate balance of cellular processes, leading to muscle damage and subsequent release of cellular CK into the bloodstream. TKIs may also affect mitochondrial function and alter ATP/ADP transport, further impacting CK levels. Other factors, including pre-existing risk factors, high-dose TKI therapy, polypharmacy, drug–drug interactions (statins), and pharmacogenetic variations, can also influence the pharmacokinetics of TKIs and increase the risk for TKI-associated CK elevation. Screening for the common rs4149056 polymorphism in *SLCO1B1* (a hepatic uptake transporter) could also be a reasonable approach when considering statins and TKIs combination treatments.[26]

In the future, several areas warrant attention regarding TKI-induced CK elevation. Further research is needed to elucidate the precise mechanisms underlying CK elevation in response to specific TKIs. Understanding these mechanisms will aid in the development of specific interventions to mitigate CK-related adverse effects. Identifying predictive markers or genetic variants associated with TKI-induced CK elevation may help personalize treatment strategies and optimize patient care. Moreover, novel therapeutic agents could be developed to mitigate muscle damage and preserve CK homeostasis. The clinical management of TKI-induced CK elevation is currently based on symptomatic management and close monitoring of serum CK levels. Enhancing patient awareness regarding TKI-induced CK elevation is vital. Regular monitoring of serum CK levels, along with clinical assessment of other potential adverse effects, can help guide treatment decisions and ensure patient safety. The presence of significant CK elevation or severe symptoms may necessitate dose adjustment, drug discontinuation, or implementation of additional interventions. Careful dose selection is of paramount importance for patients with elevated CK levels. The principles of quantitative pharmacology can be applied to ensure target inhibition while minimizing off-target inhibition in this patient population. Pharmacokinetic (PK) and pharmacodynamic (PD) studies can be used to establish the dose–response relationship and identify the optimal dose range that provides the necessary target inhibition. To this end, Gupta et al.[68] recently conducted efficacy and safety exposure-response analyses of pivotal ALTA studies to support a favorable benefit–risk profile with the approved dosing regimen (180 mg q.d. with 7-day lead-in at 90 mg) versus 90 mg q.d. of brigatinib in ALK–Positive NSCLC.

It is noteworthy that the correlation between TKI-induced serum CK elevation and the antitumor response or prognosis remains to be determined. Multiple studies investigated the relationship between elevated serum CK levels and the effectiveness of TKI therapy in different cancer types. Interestingly, CK elevation is often associated with improved overall survival (OS) and event-free survival (EFS) in CML patients receiving TKIs (such as imatinib, dasatinib, nilotinib, and bosutinib).[52] In NSCLC patients with EGFR mutations, serum CK elevation following aumolertinib is also linked to longer PFS and better treatment response.[110,117–119] Collectively, higher baseline serum CK levels and significant CK increase after TKI treatment were found to be positive prognostic indicators.[110] These suggested that the extent of CK elevation may have predictive value in both adverse effects and efficacy. In clinical setting, close monitoring of serum CK level may allow physicians to strike a balance between efficacy and adverse effect before dose adjustment or treatment discontinuation.

In summary, TKI-induced CK elevation is a prevalent adverse effect in cancer patients on targeted therapy. Serum CK level may serve as a valuable clinical biomarker for monitoring treatment response and detecting potential adverse effects. Future research should focus on unraveling the underlying mechanisms, exploring the potential of CK monitoring as a prognostic biomarker, and developing strategies to preserve CK homeostasis. Improved understanding of TKI-induced CK elevation will contribute to the development of personalized treatment strategies and enhance patient care in the era of targeted anticancer therapies.

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