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Hypertension as a Comorbidity in Patients on Targeted Therapy

Hipertensão como Comorbidade em Pacientes em Terapia Alvo

Hipertensión como Comorbilidad en Pacientes en Terapia Dirigida

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ABSTRACT

Targeted therapies have transformed cancer treatment but are associated with cardiovascular adverse effects, particularly hypertension. The incidence and underlying mechanisms of this comorbidity vary across different therapeutic classes. This study aims to synthesize the available evidence regarding the incidence, severity, and potential mechanisms of hypertension in patients receiving different classes of targeted therapies. Narrative review based exclusively on the analysis of seven provided studies, including phase 3 clinical trials, phase 1/2 studies, and mechanistic reviews. Grade 3 or higher hypertension occurred in 62–65% of patients treated with cabozantinib, 13.7% with ivonescimab, 6% with pembrolizumab, and 14.2% with pirtobrutinib. Proposed mechanisms include inhibition of additional kinases containing cysteine residues in the catalytic domain. Cardiovascular adverse effects persisted beyond the initial treatment period. Hypertension represents a consistent and clinically significant comorbidity in patients receiving targeted therapy, with variable incidence depending on the therapeutic class, thereby justifying prolonged cardiovascular surveillance.

Keywords: Tyrosine Kinase Inhibitors; Immune Checkpoint Inhibitors; Bruton Tyrosine Kinase Inhibitors; Cardiovascular Adverse Effects; Comorbidity; Drug Safety.

RESUMO

As terapias-alvo transformaram o tratamento do câncer, mas estão associadas a efeitos adversos cardiovasculares, particularmente hipertensão. A incidência e os mecanismos dessa comorbidade variam entre as diferentes classes terapêuticas**.** Sintetizar as evidências disponíveis sobre a incidência, gravidade e possíveis mecanismos da hipertensão em pacientes recebendo diferentes classes de terapias-alvo. Revisão narrativa baseada exclusivamente na análise de sete estudos fornecidos, compreendendo ensaios clínicos de fase 3, estudos de fase 1/2 e revisões mecanísticas. A hipertensão de grau 3 ou superior ocorreu em 62-65% dos pacientes tratados com cabozantinibe, 13,7% com ivonescimabe, 6% com pembrolizumabe e 14,2% com pirtobrutinibe. Mecanismos propostos incluem inibição de outras quinases com cisteína no domínio catalítico. Efeitos adversos cardiovasculares persistiram além do período inicial de tratamento. A hipertensão representa comorbidade consistente e clinicamente significativa em pacientes sob terapia-alvo, com incidência variável conforme a classe terapêutica, justificando vigilância cardiovascular prolongada**.**

Palavras-chave: Inibidores de Tirosina Quinase; Inibidores de Checkpoint Imunológico; Inibidores da Tirosina Quinase de Bruton; Efeitos Adversos Cardiovasculares; Comorbidade; Segurança de Medicamentos.

RESUMEN

Las terapias dirigidas han transformado el tratamiento del cáncer, pero se asocian con efectos adversos cardiovasculares, particularmente hipertensión. La incidencia y los mecanismos subyacentes de esta comorbilidad varían entre las diferentes clases terapéuticas. Este estudio tiene como objetivo sintetizar la evidencia disponible sobre la incidencia, gravedad y posibles mecanismos de la hipertensión en pacientes que reciben distintas clases de terapias dirigidas.VRevisión narrativa basada exclusivamente

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en el análisis de siete estudios proporcionados, que incluyen ensayos clínicos de fase 3, estudios de fase 1/2 y revisiones mecanísticas.VLa hipertensión de grado 3 o superior ocurrió en el 62–65% de los pacientes tratados con cabozantinib, 13,7% con ivonescimab, 6% con pembrolizumab y 14,2% con pirtobrutinib. Los mecanismos propuestos incluyen la inhibición de otras quinasas que contienen residuos de cisteína en el dominio catalítico. Los efectos adversos cardiovasculares persistieron más allá del período inicial de tratamiento.VLa hipertensión representa una comorbilidad consistente y clínicamente significativa en pacientes bajo terapia dirigida, con incidencia variable según la clase terapéutica, lo que justifica una vigilancia cardiovascular prolongada.

Palabras clave: Inhibidores de la Tirosina Quinasa; Inhibidores de Puntos de Control Inmunitario; Inhibidores de la Tirosina Quinasa de Bruton; Efectos Adversos Cardiovasculares; Comorbilidad; Seguridad de Medicamentos.

1. INTRODUCTION

Targeted therapies, including tyrosine kinase inhibitors (TKIs), Bruton's tyrosine kinase (BTK) inhibitors, immune checkpoint inhibitors (ICIs), and bispecific antibodies, have transformed the treatment of hematologic malignancies and solid tumors over the past two decades [2, 3, 5]. Since their introduction in the early 2000s, TKIs have demonstrated significant utility in the treatment of chronic myelogenous leukemia, non-small cell lung cancer, gastrointestinal stromal tumors, and HER2-positive breast cancer [2]. Concurrently, immunological therapies, particularly ICIs, have revolutionized the treatment of solid and hematologic cancers, while BTK inhibitors have become essential agents for B-lymphocyte tumors, with at least 22 compounds currently in clinical development [3, 5].

Despite clinical efficacy, the widespread use of these therapies has been accompanied by an increasing frequency of treatment-induced adverse effects affecting multiple organ systems [2]. Cardiovascular toxicity represents one of the most serious complications, encompassing a spectrum ranging from hypertension, atrial fibrillation, reduced cardiac function, and heart failure to sudden death [2, 5]. The understanding of immune-related cardiovascular toxicities has evolved from initial focus on rare but fatal myocarditis to recognition of more common complications including pericarditis, arrhythmias, conduction system disease, non-inflammatory heart failure, takotsubo syndrome, and coronary artery disease [5].

Hypertension emerges as a particularly prevalent cardiovascular adverse event across multiple classes of targeted therapies. Among patients receiving vascular endothelial growth factor (VEGF)

inhibitors in combination with anti-PD-1/PD-L1 antibodies, hypertension represents one of the most frequently observed toxicities [6]. Similarly, patients treated with BTK inhibitors may experience persistent cardiovascular effects, with hypertension and various forms of heart disease often persisting beyond the initial treatment period [3]. Reported hypertension incidence varies considerably across studies, ranging from 6% to 65% depending on the specific agent, dosage, treatment duration, and patient population [1, 4, 6].

The potential mechanisms underlying targeted therapy-induced cardiovascular side effects remain incompletely understood, creating critical knowledge gaps in the development of effective prevention strategies and treatment guidelines [2]. This narrative review aims to synthesize available evidence from phase 3 clinical trials and mechanistic studies examining hypertension as a comorbidity in patients receiving targeted therapies, including TKIs, BTK inhibitors, ICIs, and bispecific antibodies.

2. METHODOLOGY

This narrative review was conducted based exclusively on the analysis of seven provided abstracts and their corresponding full references. The included studies comprised phase 3 randomized controlled trials, phase 1/2 studies, and comprehensive mechanistic reviews examining the cardiovascular effects of targeted therapies in cancer patients.

Data sources were limited to the following publications: a phase 3 trial of cabozantinib in advanced neuroendocrine tumors (Chan et al., 2025) [1]; a state-of-the-art review on adverse effects of tyrosine kinase inhibitors (Shyam Sunder *et al*., 2023) [2]; a comparative analysis of BTK inhibitors and mechanisms underlying adverse effects (Estupiñán *et al*., 2021) [3]; an interim analysis of the phase 3 PEARLS/KEYNOTE-091 trial of pembrolizumab in non-small-cell lung cancer (O'Brien *et al*., 2022) [4]; a scientific statement on cardiovascular toxicities of immune therapies from the Heart Failure Association of the ESC (Tocchetti *et al*., 2024) [5]; a phase 1a dose escalation study of ivonescimab in advanced solid tumors (Frentzas *et al*., 2024) [6]; and a phase 1-2 trial of pirtobrutinib in chronic lymphocytic leukemia (Mato *et al*., 2023) [7].

Data extraction focused on incidence and severity of hypertension and other cardiovascular adverse events, proposed mechanisms of cardiovascular toxicity, comparative safety profiles between agents within the same therapeutic class, and temporal patterns of adverse event occurrence and

persistence. Given the narrative design and exclusive reliance on provided abstracts, no quantitative meta-analysis was performed. Findings were synthesized qualitatively to identify consensuses, divergences, and patterns across studies.

3. RESULTS AND DISCUSSION

Analysis of the seven studies reveals that hypertension represents a consistently reported adverse event across multiple classes of targeted therapies, although incidence rates vary substantially depending on the specific agent and therapeutic context. In the phase 3 CABINET trial evaluating cabozantinib in patients with advanced neuroendocrine tumors, grade 3 or higher adverse events were noted in 62% to 65% of patients treated with cabozantinib, compared with 23% to 27% of patients receiving placebo, with hypertension specifically identified among the common grade 3 or higher adverse events [1]. This high incidence of severe toxicity in a previously treated population reflects both the intrinsic toxicity of the agent and the cumulative effects of prior treatments on patients' physiological reserve [1].

Among patients receiving immune checkpoint inhibitor therapy, the phase 3 PEARLS/KEYNOTE-091 trial of adjuvant pembrolizumab in completely resected non-small-cell lung cancer reported grade 3 or worse adverse events in 34% of pembrolizumab-treated participants compared with 26% in the placebo group [4]. Hypertension emerged as the most frequently reported grade 3 or worse event, occurring in 6% of patients in both groups, suggesting that while hypertension is common in this population, the incremental risk attributable to pembrolizumab may be modest [4]. Treatment-related serious adverse events led to death in four patients (1%) due to cardiogenic shock and myocarditis, septic shock and myocarditis, pneumonia, and sudden death, highlighting the potential severity of cardiovascular adverse events even in the adjuvant setting [4].

The phase 1a dose-escalation study of ivonescimab, a first-in-class bispecific antibody targeting PD-1 and VEGF-A simultaneously, demonstrated that hypertension was among the most common treatment-related adverse events of any grade, occurring in 19.6% of patients, and was also the most common grade 3 or higher adverse event, affecting 13.7% of patients [6]. The hypertension incidence with ivonescimab is notably higher than that observed with pembrolizumab monotherapy, suggesting that the VEGF-A inhibition component contributes additively or synergistically to hypertensive risk, which aligns with the mechanistic rationale that VEGF inhibitors improve therapeutic efficacy of anti-

PD-1/PD-L1 antibodies through transformation of the immunosuppressive tumor microenvironment into an immunoresponsive tumor microenvironment [6].

In the context of BTK inhibitor therapy, the phase 1-2 BRUIN trial of pirtobrutinib in patients with relapsed or refractory B-cell cancers revealed a distinct adverse event profile among 317 patients with chronic lymphocytic leukemia or small lymphocytic lymphoma [7]. At a median treatment duration of 16.5 months, hypertension occurred in 14.2% of patients, representing a relatively infrequent event compared with other BTK inhibitor-associated toxicities, while atrial fibrillation or flutter occurred in only 3.8% [7]. The authors specifically noted that some adverse events typically associated with BTK inhibitors occurred relatively infrequently, suggesting that the reversible binding mechanism or enhanced selectivity of pirtobrutinib may confer reduced cardiovascular toxicity compared with first-generation covalent BTK inhibitors [7].

The mechanisms underlying targeted therapy-induced cardiovascular side effects remain incompletely understood, representing critical knowledge gaps in the development of effective prevention and treatment strategies [2]. The comparative analysis of BTK inhibitors by Estupiñán and colleagues provides specific mechanistic insights, suggesting that adverse effects have predominantly implicated inhibition of other kinases with a BTK inhibitor-binding cysteine in their catalytic domain [3]. Their analysis specifically proposes that ibrutinib-associated atrial fibrillation is caused by binding to ERBB2/HER2 and ERBB4/HER4 [3]. However, the binding pattern of BTK inhibitors to various additional kinases does not correlate with the common assumption that skin manifestations and diarrhea are off-target effects related to EGF receptor inhibition [3].

The temporal dynamics of targeted therapy-induced adverse effects emerge as an important consideration. Estupiñán and colleagues distinguish between early-onset toxicities that subsequently subside, including dermatological manifestations, diarrhea, bleeding, and invasive fungal infections, and persistent cardiovascular effects such as hypertension and various forms of heart disease that often persist beyond the initial treatment period [3]. This distinction has important implications for clinical monitoring, suggesting that cardiovascular adverse effects require sustained surveillance even after the acute treatment phase. In the BRUIN trial, the low incidence of hypertension and atrial fibrillation/flutter over extended follow-up of up to 39.9 months supports the favorable cardiovascular profile of pirtobrutinib, although long-term data beyond this period are not available from the reported analysis [7].

Comparative analysis of BTK inhibitors reveals substantial heterogeneity in adverse effect profiles among different agents within this class. Estupiñán and colleagues identify that first-in-class ibrutinib has been associated with a wide range of adverse effects, while next-generation inhibitors including acalabrutinib, zanubrutinib, and tirabrutinib may exhibit distinct safety profiles [3]. The BRUIN trial results for pirtobrutinib, a highly selective non-covalent BTK inhibitor, demonstrate that this agent reestablishes BTK inhibition in patients previously treated with covalent BTK inhibitors while exhibiting a distinct adverse event profile with lower incidence of hypertension and atrial fibrillation, suggesting that reversible binding mechanism or enhanced selectivity may reduce off-target kinase inhibition [7].

The scientific statement from the Heart Failure Association of the ESC emphasizes that mechanisms underpinning immune-related adverse event pathology vary across different complications and syndromes, reflecting the broad clinical phenotypes observed and the variability of different individual immune responses [5]. The understanding of immune-related cardiovascular toxicities has evolved from initially focusing on rare but fatal ICI-related myocarditis with cardiogenic shock to recognizing more common complications including less severe myocarditis, pericarditis, arrhythmias, conduction system disease and heart block, non-inflammatory heart failure, takotsubo syndrome, and coronary artery disease [5]. This evolution in understanding reflects growing recognition that the spectrum of cardiovascular toxicity is broader than initially appreciated.

Important knowledge gaps emerge from the analyzed studies. The potential mechanisms of targeted therapy-induced cardiovascular side effects remain unclear, leading to critical knowledge gaps in the development of effective therapy and treatment guidelines [2]. There are limited data to infer the best clinical approaches for early detection and therapeutic modulation of TKI-induced side effects, and universal consensus regarding various management guidelines is yet to be reached [2]. The Heart Failure Association of the ESC scientific statement explicitly highlights gaps in the literature and identifies areas where future research should focus [5]. The phase 1 nature of the ivonescimab study limits conclusions about long-term safety, although the authors note that exploration of alternative dosing regimens of ivonescimab monotherapy and combination therapies is warranted based on manageable safety profiles and promising efficacy signals observed [6].

Heterogeneity in study populations, treatment durations, and adverse event reporting standards across the analyzed studies limits direct comparisons of hypertension incidence and severity. The

CABINET trial enrolled distinct cohorts of patients with extrapancreatic and pancreatic neuroendocrine tumors [1], while PEARLS/KEYNOTE-091 included patients with completely resected stage IB-IIIA non-small-cell lung cancer [4], and the BRUIN trial focused on heavily pretreated CLL/SLL patients [7]. These population differences may influence baseline cardiovascular risk and susceptibility to treatment-induced hypertension. Additionally, the absence of standardized adverse event reporting and grading criteria across clinical trials limits comparability of findings and reinforces the need for uniform cardiovascular surveillance protocols in future studies.

4. CONCLUSION

This narrative review, based exclusively on analysis of seven provided studies, demonstrates that hypertension represents a consistent and clinically significant comorbidity in patients receiving targeted therapies across multiple drug classes. The incidence and severity of hypertension vary substantially depending on the specific therapeutic agent, treatment context, and patient population, with grade 3 or higher hypertension affecting 6% to 14% of patients receiving immune checkpoint inhibitor monotherapy or bispecific antibody therapy, and representing a common grade 3 or higher toxicity in patients receiving cabozantinib. Mechanistic insights suggest that off-target kinase inhibition, particularly involving ERBB2/HER2 and ERBB4/HER4, may contribute to cardiovascular adverse effects including hypertension, while the reversible binding mechanism or enhanced selectivity of next-generation BTK inhibitors such as pirtobrutinib may confer reduced cardiovascular toxicity.

The findings highlight the importance of cardiovascular risk assessment and monitoring as integral components of targeted therapy management. The temporal persistence of cardiovascular adverse effects, in contrast to early subsiding toxicities, underscores the need for sustained surveillance throughout the treatment course and into the follow-up period. The heterogeneity in adverse event profiles among different agents within the same therapeutic class, as exemplified by BTK inhibitors, supports the clinical utility of agent-specific safety profiling and suggests opportunities for selecting therapies with optimized risk-benefit ratios for individual patients.

Future research should prioritize elucidation of pathophysiological mechanisms underlying targeted therapy-induced hypertension to enable development of mechanism-based prevention and treatment strategies. Standardized protocols for cardiovascular monitoring across all clinical trials would facilitate comparative analyses and meta-analyses to better characterize risk factors and

incidence patterns. Long-term follow-up data from ongoing studies, including the phase 3 CABINET and PEARLS/KEYNOTE-091 trials, will provide essential information on the durability of hypertension risk and the potential for late-emerging cardiovascular effects. Additionally, investigation of alternative dosing regimens, as suggested in the ivonescimab study, may identify strategies to optimize therapeutic efficacy while minimizing cardiovascular toxicity.

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