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Occurrence and Time-To-Onset of Cytomegalovirus Infection in Patients Treated with First- and Second-Generation Bruton's Tyrosine Kinase Inhibitors: A Retrospective Analysis of Data from The Japanese Adverse Drug Event Report Database

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Abstract

Background: Burton's tyrosine kinase inhibitors (BTKis) are used to treat hematological malignancies. However, serious adverse events (AEs)—myelosuppression, bleeding, cardiovascular AEs, and infections including cytomegalovirus (CMV) infection—are of concern in immunocompromised individuals with hematological malignancies and individuals with post-transplant complications. Currently, there is a lack of reports of AEs associated with these novel molecular targeted drugs. We aimed to detect signals of CMV infection in patients treated with BTKis and assess their influence on time-to-onset of the infection using data from the Japanese Adverse Drug Event Report (JADER) database.

Methodology: In this retrospective study, individual reporting odds ratios (RORs) were calculated to assess CMV infection signals in patients receiving ibrutinib, tirabrutinib, or acalabrutinib. A CMV infection signal was considered present when the ROR confidence interval exceeded 1. The duration of CMV infection was determined by calculating the number of days from the onset of the AE to start of drug administration.

Results: There were 13 cases of CMV infection, and AE signals were observed only in patients receiving ibrutinib. In five cases where time-to-onset could be analyzed, the median duration of CMV infection was 154 (72–168) days, with the duration in one case exceeding 200 days. Reported outcomes were improvement in three cases, recovery in six, death in two, and unknown in two.

Conclusion: An AE signal was detected for ibrutinib. However, the low number of events and differing exposure durations among patients receiving BTK inhibitors precluded definitive comparative safety conclusions; further accumulation of AE data is warranted.

Keywords: Adverse-event signal, Bruton's tyrosine kinase inhibitor, ibrutinib, cytomegalovirus infection

Introduction

Burton's tyrosine kinase (BTK) is a cytoplasmic receptor protein kinase that acts downstream of membrane receptors such as the B-cell receptor (BCR), Toll-like receptor, and C-X-C chemokine receptor type 4. BTK plays a key role in activating the BCR and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling pathways. BTK inhibitors (BTKis) exert

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antitumor effects by covalently binding to the C481 residue of BTK, thus inhibiting the downstream NFκB pathway, which is constitutively activated by genetic abnormalities [1]. BTKis are effective and indicated for the treatment of chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström macroglobulinemia/lymphoplasmacytic lymphoma, primary central nervous system lymphoma, and other diseases. However, despite their therapeutic benefit, the use of these targeted agents has been associated with an increased risk of invasive infections [2].

Human cytomegalovirus (CMV), a DNA virus belonging to the herpesvirus family, poses a serious threat to specific populations, particularly individuals with immunosuppression or hematological disorders. In these individuals, acute CMV infection substantially increases the risk of morbidity and mortality [3]. Moreover, it has been associated with the development of malignant lymphoma [4,5], occasionally leading to severe outcomes. Therefore, among the various infectious complications that arise early after transplantation, CMV infection warrants particular attention. Although viral detection methods and antiviral therapies have already been established, delayed or missed detection may cause systemic dissemination of CMV infection to multiple organs, such as the liver and lungs, gastrointestinal tract, and retina. Therefore, careful attention and management of CMV infection are required. Recent advances in pharmacovigilance have improved the detection of drug-associated adverse event (AE) signals using data from large databases such as the Japanese Adverse Drug Event Report (JADER), which are based on spontaneous AE reports [6]. Evaluation of drug-associated AE signals involves disproportionality analysis, including the calculation of reporting odds ratios (RORs) and information components (ICs) in pharmacovigilance activity [7]. The JADER, a Japanese nationwide open-access database, compiles spontaneous AE reports from the Pharmaceuticals and Medical Devices Agency (PMDA), a pharmaceutical regulatory authority in Japan.

Although several case reports have described central nervous system aspergillosis and cryptococcosis associated with CMV pneumonia in patients with chronic lymphocytic leukemia treated with acalabrutinib [8], reports of CMV infection in patients receiving BTKis in clinical practice remain limited. Moreover, the occurrence of CMV infection signals in patients treated with BTKis has not been clarified. In addition, the JADER database currently does not contain reports detailing the clinically important interval between BTKi treatment initiation and CMV infection onset. In this study, we aimed to investigate CMV infection signals in patients receiving BTKi therapy using data from the JADER database, further examining the time to CMV infection onset in this population.

Methods

Data source

Data from the JADER database, spanning April 2004 to December 2025, were obtained from the PMDA website [9]. The JADER dataset includes four tables: demographic information ("demo"), drug information ("drug"), AE information ("reac"), and medical history ("Hist"). It contains data on 1,002,922 patients, with 4,879,558 cases and 1,661,502 AEs. The "demo" table presents patient demographic data, including sex and age. Patients with blank or unknown sex or age data in the "demo" table, as well as notifications containing duplicate entries in the "drug," "reac," and "hist" tables, were excluded. The "demo" table data were then linked to data in the "drug," "reac," and "hist" tables using patient identification numbers. After data cleaning, data of 878,971 patients were analyzed in the present study (Fig 1).

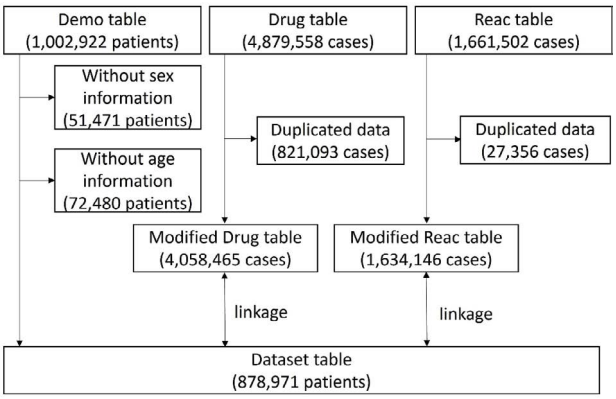

Figure 1: Flow diagram of the study

CMV infections were identified from the "reac" table using preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA, 28.1J). Twenty-seven PTs, categorized under the high-level term (HLT) "Cytomegaloviral infections" (HLT code 10011827), were used to define CMV infections (Table 1).

Table 1: Definition of cytomegalovirus infections

HLT code	**HLT name**
10011827	Cytomegaloviral infections
PT code	**PT name**
10010430	Congenital cytomegalovirus infection
10011830	Cytomegalovirus hepatitis
10011831	Cytomegalovirus infection
10011834	Cytomegalovirus mononucleosis
10014586	Encephalitis cytomegalovirus
10035676	Pneumonia cytomegaloviral

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10048843	Cytomegalovirus chorioretinitis
10048983	Cytomegalovirus colitis
10049014	Cytomegalovirus duodenitis
10049015	Cytomegalovirus enterocolitis
10049016	Cytomegalovirus gastritis
10049018	Cytomegalovirus esophagitis
10049074	Cytomegalovirus enteritis
10049075	Disseminated cytomegaloviral infection
10049566	Cytomegalovirus pancreatitis
10051349	Cytomegalovirus gastroenteritis
10051350	Cytomegalovirus urinary tract infection
10052817	Cytomegalovirus gastrointestinal infection
10056261	Cytomegalovirus myocarditis
10056262	Cytomegalovirus syndrome
10056721	Cytomegalovirus pericarditis
10058666	Cytomegalovirus infection reactivation
10058854	Cytomegalovirus viraemia
10065036	Cytomegalovirus mucocutaneous ulcer
10065621	Cytomegalovirus myelomeningoradiculitis
10075619	Cytomegalovirus gastrointestinal ulcer
10079095	Cytomegalovirus nephritis

HLT: high level term; PT: preferred term.

Signal detection

This study employed the ROR and IC for CMV infection signal detection, as previously described [10–13]. The ROR serves as an AE signal index, representing the odds of reporting a specific AE versus all other AEs associated with the target drugs compared to the odds for all other drugs. Accordingly, RORs may be inherently unreliable when the sample size is small. Conversely, IC, an adverse drug reaction signal index from Bayesian Confidence Propagation Neural Network analysis, can detect AE signals even with a small sample size [10,14]. Here, RORs, ICs, and their 95% confidence intervals (CIs) were calculated using a two-by-two contingency table (Table 2) and the following equations [15]:

ROR equations:

$$\mathrm{ROR} = \frac{N_{11}/N_{01}}{N_{10}/N_{00}} = \frac{N_{11}N_{00}}{N_{10}N_{01}}$$

$$\mathrm{ROR}(95\%\ \mathrm{CI}) = e^{\ln(\mathrm{ROR})\pm 1.96\sqrt{\frac{1}{N_{11}}+\frac{1}{N_{10}}+\frac{1}{N_{01}}+\frac{1}{N_{00}}}}$$

IC Equations:

$$E(\mathrm{IC}_{11}) = \log_2 \frac{(N_{11}+\gamma_{11})(N_{++}+\alpha)(N_{++}+\beta)}{(N_{++}+\gamma)(N_{1+}+\alpha_1)(N_{+1}+\beta_1)}$$

$$V(\mathrm{IC}_{11}) = \left(\frac{1}{\ln 2}\right)^2 \left[\frac{N_{++}-N_{11}+\gamma-\gamma_{11}}{(N_{11}+\gamma_{11})(1+N_{++}+\gamma)} + \frac{N_{++}-N_{1+}+\alpha-\alpha_1}{(N_{1+}+\alpha_1)(1+N_{++}+\alpha)} + \frac{N_{++}-N_{+1}+\beta-\beta_1}{(N_{+1}+\beta_1)(1+N_{++}+\beta)}\right]$$

$$\gamma = \gamma_{11}\frac{(N_{++}+\alpha)(N_{++}+\beta)}{(N_{1+}+\alpha_1)(N_{+1}+\beta_1)},\ \gamma_{11} = 1,\ \alpha_1 = \beta_1 = 1,\ \alpha = \beta = 2$$

$$\mathrm{IC}(95\%\ \mathrm{CI}) = E(\mathrm{IC}_{11}) \pm 2\sqrt{V(\mathrm{IC}_{11})}\ .$$

All calculations were performed using Microsoft Excel Microsoft Japan Co., Ltd Tokyo, Japan). Signals were positive if the 95% CI lower limit of ROR exceeded 1 and IC exceeded 0.

Time-to-onset analysis

Time-to-onset a 1 nalysis was performed using data from the point of initial treatment with ibrutinib (IBR), tirabrutinib (TIR), or acalabrutinib (ACR) in the "drug" table to the date of the first CMV infection occurrence in the "reac" table. Patients with missing or inaccurate data on the dates of initial BTKi treatment and CMV infection were excluded. All calculations were conducted using Microsoft Excel (Microsoft Japan Co., Ltd., Tokyo, Japan). CMV infection onset was calculated by subtracting the date of initial treatment commencement from the date of CMV infection onset.

Results

CMV infection signal under BTKi treatment

The RORs and ICs for CMV infections during BTKi treatment are presented in Table 3. All BTKis—IBR, TIR, and ACR—were included in the analysis. Significant AE signals were detected only in the IBR-treated cohort.

Patient details, their background, and outcomes of CMV infections

Table 4 presents information on the sex, age, time interval

Table 3: Reporting odds ratios (RORs) and information components (ICs) of cytomegalovirus (CMV) infections following administration of Bruton's tyrosine kinase inhibitors.

Drug	CMV infection (cases)	Total AEs (cases)	ROR	95% CI	IC	95% CI
Ibrutinib	13	880	2.02	1.17–3.50	0.9	0.12 to 1.68
Tirabrutinib	0	443	N.D.	N.D.	N.D.	N.D.
Acalabrutinib	1	115	1.18	0.16–8.46	0.11	-1.95 to 2.17

CMV, cytomegalovirus; AE, adverse event; ROR, reporting odds ratio; CI, confidence interval; IC, information component, N.D.; not detected.

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from IBR administration to CMV infection onset date, PT detection date, and clinical outcome for 13 cases of CMV infection defined by PT. Among the 13 cases, the clinical outcomes were improvement, recovery, death, and unknown in 3, 6, 2, and 2 cases, respectively. Although the timing of these complications was unclear, one of the two fatal cases was complicated by CMV pneumonia and CMV pancreatitis.

Time-to-onset analysis

Overall, 13 cases were analyzed, excluding 8 cases with unknown details. In the time-to-onset analysis, the median period [interquartile range] for CMV infection onset in patients receiving IBR treatment was 154 [72–168] days. The detailed time-to-onset data are presented in Table 4.

Discussion

Among the 13 detected cases in this study, several were classified as serious, including two reported deaths, highlighting the need for careful monitoring of CMV infection in patients treated with IBR, a novel targeted molecular therapy. BTKis exert antitumor effects by covalently binding to the C481 residue of BTK, inhibiting the NFκB pathway constitutively activated by genetic abnormalities. Second-generation and later BTKis, including TIR, ACR, and zanubrutinib, are considered to exhibit greater kinase selectivity than IBR, a first-generation BTKi, resulting in fewer off-target effects [1]. In the present study, CMV infection signals were detected only in patients receiving IBR among all available BTKis. Although CMV infection is not a common infectious complication associated with IBR use, our findings may reflect an adverse consequence of the broad inhibitory activity of IBR against multiple tyrosine kinases. Furthermore, BTKis are novel molecularly targeted agents, and additional accumulation of spontaneously reported AEs is warranted. In addition, the AE profiles of BTKis may include several as-yet unidentified toxicities, underscoring the importance of long-term monitoring. Reddy et al. reported the case of an 88-year-old patient with chronic lymphocytic leukemia receiving IBR therapy who presented with painless hematochezia lasting 2 days, with bright red blood observed on digital rectal examination. Laboratory findings revealed a marked decrease in serum hemoglobin level. Biopsy of a rectal ulcer was positive for CMV immunostaining. The patient was treated with intravenous ganciclovir, followed by a switch to valganciclovir, for a total of 21 days of antiviral therapy. Ultimately, the patient's symptoms improved, and the clinical outcome was favorable [16].

Patients treated with BTKis are at a high risk of developing hypogammaglobulinemia owing to impairment of the humoral immunity resulting from suppression of B-cell proliferation by BTKis [17–19]. In addition, previous studies have indicated that intracellular Th2 cytokine level decreases during the first 6–12 months after the initiation of IBR treatment, leading to a decrease in regulatory T cell count and a potential increase in opportunistic infection risk during this period [20,21]. CMV infection is a latent herpesvirus infection that can be reactivated in immunosuppressed hosts, such as patients with hematologic malignancies and transplant

Table 4: Details of patients with CMV infection treated with ibrutinib and clinical outcomes.

No.	Sex	Age	CMV infection onset (days)	PT	Outcome
1	Female	60s	72	Cytomegalovirus infection	Recovery
2	Male	70s	154	Cytomegalovirus infection	Improvement
3	Male	60s	168	Pneumonia cytomegaloviral	Recovery
4	Male	70s	233	Cytomegalovirus chorioretinitis	Recovery
5	Male	80s	61	Cytomegalovirus enterocolitis	Recovery
6	Male	60s	unknown	Cytomegalovirus infection	Death
7	Female	70s	unknown	Pneumonia cytomegaloviral/Cytomegalovirus pancreatitis	Death
8	Male	20s	unknown	Cytomegalovirus infection	Improvement
9	Male	70s	unknown	Cytomegalovirus enterocolitis	Recovery
10	Male	80s	unknown	Cytomegalovirus infection	Unknown
11	Male	80s	unknown	Cytomegalovirus enterocolitis	Recovery
12	Female	70s	unknown	Cytomegalovirus infection reactivation	Improvement
13	Female	70s	unknown	Cytomegalovirus infection reactivation	Unknown

PT, preferred term.

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recipients, increasing the risk of morbidity and mortality. Therefore, early diagnosis of CMV infection and prompt initiation of antiviral therapy are considered essential for preventing clinical deterioration and improving prognosis in these patients and other high-risk groups, such as older adults in their 80s, as observed in our study [21,22]. In our study, there was also a fatal case complicated by CMV pneumonia and pancreatitis. As delayed detection of CMV infection may allow progression to systemic infection involving multiple organs, the early detection of CMV infection should be an important consideration in clinical practice.

In some patients with hematologic malignancies, T-cell function may already be impaired either because of the underlying disease itself or treatment history; this impairment can increase the risk of CMV reactivation. In such patients, administration of agents such as IBR, which may further suppress both B-cell and T-cell functions and thereby alter cellular immunity, is considered likely to further increase CMV infection risk [23]. Our study has some limitations that are worth mentioning. First, the JADER database is a spontaneous reporting system, which is inherently passive and subject to biases, including under-reporting, over-reporting, and confounding by comorbidities. Second, the characteristics of the JADER database make it challenging to assess the number of treatment courses and chemotherapy drug dosage. Finally, the time-to-onset analysis had a small number of CMV infection cases and therefore, caution is required when interpreting the results.

Conclusion

A CMV infection signal was detected in patients receiving IBR; however, the low number of events and differing exposure durations among patients receiving BTK inhibitors precluded definitive comparative safety conclusions. As BTKis are novel targeted therapeutic agents, further accumulation of AE data is warranted.

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Conflicts of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contribution statement

Kaori Ito and Koki Kato designed the study. Kaori Ito, Koki Kato, and Misaki Morisaku conducted data analysis. Shigeki Yamada and Nobuki Hayakawa supervised the study. Kaori Ito, Koki Kato, and Misaki Morisaku drafted the manuscript. Shigeki Yamada and Nobuki Hayakawa reviewed and edited the manuscript. All authors approved the final manuscript.

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