Risk Factors for Ganciclovir-Induced Thrombocytopenia and Leukopenia

Kazuaki Matsumoto, a Akari Shigemi, a Kazuro Ikawa, b Naoko Kanazawa, a Yuko Fujisaki, a Norifumi Morikawa, a and Yasuo Takeda * a,b

a Department of Clinical Pharmacy and Pharmacology, Graduate School of Medical and Dental Sciences, Kagoshima University; 8–35–1 Sakuragaoka, Kagoshima 890–8520, Japan; and b Department of Clinical Pharmacotherapy, Hiroshima University; 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan.

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Ganciclovir is a nucleoside guanosine analogue that exhibits therapeutic activity against human cytomegalovirus infection, and is primarily excreted via glomerular filtration and active tubular secretion. The adverse effects induced by ganciclovir therapy are generally of a hematological nature and include thrombocytopenia and leukopenia. Low marrow cellularity and elevated serum creatinine have been identified as risk factors for ganciclovir-induced neutropenia. However, the risk factors for thrombocytopenia have yet to be determined. Therefore, this study investigated patients administered ganciclovir to determine the risk factors for thrombocytopenia and leukopenia. Thrombocytopenia occurred in 41 of these patients (30.6%).

Multivariate logistic regression analysis identified three independent risk factors for thrombocytopenia: cancer chemotherapy (odds ratio (OR)=3.1), creatinine clearance (<20 mL/min) (OR=12.8), and the ganciclovir dose (≥12 mg/kg/d) (OR=15.1). Leukopenia occurred in 36 patients (28.6%), and white blood cell count (<6000 cells/mm³) (OR=3.7) and the ganciclovir dose (≥12 mg/kg/d) (OR=7.8) were identified as risk factors.

These results demonstrated that several factors influenced the occurrence of ganciclovir-induced thrombocytopenia and leukopenia, and suggest that special attention should be paid to patients receiving cancer chemotherapy with a low creatinine clearance (<20 mL/min) and high dose (≥12 mg/kg/d) in order to avoid ganciclovir-induced thrombocytopenia.

Key words ganciclovir; thrombocytopenia; leukopenia

Ganciclovir is a nucleoside guanosine analogue that exhibits therapeutic activity against human cytomegalovirus infection. Intravenous ganciclovir is usually administered at a dose of 5 mg/kg every 12 h (10 mg/kg/d) for 14 to 21 d. The elimination half-life and total plasma clearance following the administration of intravenous ganciclovir were previously reported to be approximately 6.0 h and 0.2 L/h/kg, respectively. Ganciclovir is primarily excreted via glomerular filtration and active tubular secretion; therefore, renal dysfunction reduces the elimination of the drug, thereby necessitating dosage reductions.

The adverse effects induced by ganciclovir therapy are generally of a hematological nature and include thrombocytopenia and leukopenia. Studies reported that the incidences of thrombocytopenia and leukopenia induced by ganciclovir were 5–41% and 7–68%, respectively. Three studies have so far identified risk factors for ganciclovir-induced neutropenia. Tomonari et al. reported that reduced renal function was a risk factor for ganciclovir-induced neutropenia. Nakanishi et al. reported a decrease in the platelet count to <130000 cells/mm³ before ganciclovir therapy, suggesting that low marrow cellularity and elevated serum creatinine were risk patients. Thus, the present study examined patients being administered ganciclovir in order to determine the risk factors for drug-induced thrombocytopenia and leukopenia.

PATIENTS AND METHODS

Patients This study was approved by the Ethics Review Board of Kagoshima University Hospital (#408). This study retrospectively assessed data obtained between January 2006 and December 2010 for 185 adult patients who received ganciclovir at Kagoshima University Hospital. Information including platelet counts, white blood cell (WBC) counts, and serum creatinine concentrations was extracted from electronic medical records. The presence or absence of cancer chemotherapy was examined within 14 d before and during ganciclovir therapy. The dose of ganciclovir was adjusted for each patient according to their rate of creatinine clearance.

Assessment of Thrombocytopenia Data obtained for 134 patients were used to assess thrombocytopenia; 51 patients were excluded because they had received platelet transfusions during ganciclovir therapy. Thrombocytopenia was defined as a decrease in the platelet count to <130000 cells/mm³ according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). If the platelet count was <130000 cells/mm³ before ganciclovir therapy, thrombocytopenia was defined as a decrease in the platelet count to <130000 cm³.
count to ≤75% that prior to the treatment.

**Assessment of Leukopenia** Data obtained for 126 patients were used to assess leukopenia; 51 patients were excluded because they had received platelet transfusions during ganciclovir therapy. Leukopenia was defined as a decrease in the WBC count to <4500 cells/mm³ before treatment. Leukopenia occurred in 36 patients (28.6%) and developed 12.8 ± 6.2 d after the initiation of ganciclovir. The characteristics of patients with and without leukopenia were compared. Four variables associated with the occurrence of leukopenia were identified by univariate analysis: duration of treatment, age, cancer chemotherapy, WBC count (<6000 cells/mm³), and dose (≥12 mg/kg/d) (Table 2). Multivariate logistic regression analysis identified two independent risk factors for leukopenia: cancer chemotherapy (OR=3.1), and creatinine clearance (<20 mL/min) (OR=12.8), and dose (≥12 mg/kg/d) (OR=15.1) (Table 3).

**DISCUSSION**

The present study showed that adult patients administered receiving cancer chemotherapy, platelet count (<200000 cells/mm³), and creatinine clearance (<20 mL/min) at the start of treatment, and dose (≥12 mg/kg/d) (Table 2). Multivariate logistic regression analysis identified three independent risk factors for thrombocytopenia: cancer chemotherapy (OR=3.1), creatinine clearance (<20 mL/min) (OR=12.8), and dose (≥12 mg/kg/d) (OR=15.1) (Table 3).

Leukopenia occurred in 36 patients (28.6%) and developed 12.8 ± 6.2 d after the initiation of ganciclovir. The characteristics of patients with and without leukopenia were compared. Four variables associated with the occurrence of leukopenia were identified by univariate analysis: duration of treatment, age, cancer chemotherapy, WBC count (<6000 cells/mm³), and dose (≥12 mg/kg/d) (OR=7.8) (Table 5).

**RESULTS**

Patient characteristics are shown in Table 1. One hundred and eight men and 77 women, with a mean age of 54.3 ± 16.3 years (mean ± S.D.) and body weight of 51.4 ± 9.0 kg, were evaluated in the present study. Creatinine clearance was estimated to be 101.6 ± 56.2 mL/min using the Cockcroft–Gault formula. The mean ± S.D. dose of ganciclovir was 8.6 ± 2.8 mg/kg/d and the mean ± S.D. duration of treatment was 12.2 ± 6.3 d.

Thrombocytopenia occurred in 41 patients (30.6%) and developed 12.6 ± 6.3 d after the initiation of ganciclovir. The characteristics of patients with and without thrombocytopenia were compared. Four variables associated with the occurrence of thrombocytopenia were identified by univariate analysis:

**Table 1. Characteristics of the 185 Patients Included in This Study**

| Characteristics                  | Number or mean±S.D. (range) |
|----------------------------------|-----------------------------|
| Sex                              |                             |
| Male: female                     | 108:77                      |
| Age (years)                      | 54.3 ± 16.3 (16–83)         |
| Body weight (kg)                 | 51.4 ± 9.0 (31.3–78.8)      |
| Creatinine clearance (mL/min)    | 101.6 ± 56.2 (13.4–393.7)   |
| Ganciclovir dose (mg/kg/d)       | 8.6 ± 2.8 (0.5–16.0)        |
| Duration of treatment (d)        | 12.2 ± 6.3 (4–37)           |
| Underlying disease               |                             |
| Hematological malignancies       | 94                          |
| Autoimmune disease               | 30                          |
| Solid tumors                     | 15                          |
| Acquired immunodeficiency syndrome | 10                      |
| Ulcerative colitis               | 7                           |
| Others                           | 29                          |

**Table 2. Risk Factors Identified for Ganciclovir-Induced Thrombocytopenia by Univariate Analysis**

| Risk factors                                | Patients with thrombocytopenia (n=41) | Patients without thrombocytopenia (n=93) | p Value |
|---------------------------------------------|---------------------------------------|------------------------------------------|---------|
| Sex (male)                                  | 26 (63.4%)                            | 48 (51.6%)                               | 0.21    |
| Age (mean±S.D.)                             | 54.8 ± 16.3                           | 55.5 ± 17.1                              | 0.83    |
| Cancer chemotherapy                         | 14 (34.1%)                            | 16 (17.2%)                               | <0.05   |
| Use of steroids                             | 34 (82.9%)                            | 73 (78.5%)                               | 0.37    |
| Platelet count (<200000 cells/mm³)         | 40 (97.6%)                            | 46 (49.5%)                               | <0.01   |
| Creatinine clearance (<20 mL/min)           | 4 (9.8%)                              | 1 (1.1%)                                 | <0.05   |
| Ganciclovir dose (≥12 mg/kg/d)              | 4 (9.8%)                              | 1 (1.1%)                                 | <0.05   |
| Duration of treatment (d)                   | 12.6 ± 6.3                            | 12.8 ± 6.4                               | 0.89    |

**Table 3. Risk Factors Identified for Ganciclovir-Induced Thrombocytopenia by Multivariable Logistic Regression Analysis**

| Risk factors                                | Odds ratio | 95% CI        | p Value |
|---------------------------------------------|------------|---------------|---------|
| Cancer chemotherapy                         | 3.1        | 1.3–7.4       | <0.05   |
| Creatinine clearance (<20 mL/min)           | 12.8       | 1.3–122.0     | <0.05   |
| Ganciclovir dose (≥12 mg/kg/d)              | 15.1       | 1.6–142.5     | <0.05   |

CI: confidence interval.
Reduced renal function has been shown to prolong the half-life of ganciclovir. \( \text{12,13} \) Perrottet et al. \( \text{12,13} \) reported a correlation between estimates of the area under the ganciclovir concentration–time curve (AUC) and the occurrence of leukopenia. \( \text{14} \) Kanda et al. also showed that the total amount of ganciclovir and possibly the duration of high-dose ganciclovir may affect the incidence of neutropenia. \( \text{15} \) Furthermore, the predicted incidences of neutropenia of 15% and 20% were associated with AUC of 39 and 61 \( \mu g/\text{h/mL} \), respectively. \( \text{7} \) The predicted incidences of leukopenia of 40% and 50% were associated with AUC of 34 and 62 \( \mu g/\text{h/mL} \), respectively. \( \text{7} \) Thus, regarding the impact of a low creatinine clearance (<20mL/min) and high ganciclovir dose (≥12mg/kg/d) on ganciclovir-induced thrombocytopenia and leukopenia, we presumed that the poor elimination of ganciclovir led to higher bone marrow toxicity due to the accumulation of ganciclovir. Nevertheless, the relationship between the adverse effects of ganciclovir and drug exposure has not yet been investigated; therefore, further pharmacokinetic–pharmacodynamic studies are needed to elucidate the underlying mechanism in more detail and to obtain more useful dose information.

Salzberger et al. identified ganciclovir-induced neutropenia in allogeneic marrow transplant recipients as an independent predictor of poor survival. \( \text{9} \) Ganciclovir-induced neutropenia has been associated with increased rates of bacterial sepsis and invasive fungal infection in allogeneic marrow transplant recipients. \( \text{16,17} \) Thus, ganciclovir-induced neutropenia is a dose-limiting toxicity that should be avoided as much as possible. In the present study, the risk factors for ganciclovir-induced leukopenia were a low WBC count (<6000 cells/mm\(^3\)) and high ganciclovir dose (≥12mg/kg/d) (Table 5). Our results regarding a low WBC count as a risk factor for ganciclovir-induced leukopenia are consistent with the findings of previous studies. \( \text{8–10} \) Therefore, special attention should be paid to patients with low WBC counts (<6000 cells/mm\(^3\)) receiving a high ganciclovir dose (≥12mg/kg/d).

The usual dose of intravenous ganciclovir is 5mg/kg every 12h (10mg/kg/d) in patients with normal renal function. However, in this retrospective study, \( \text{i.e.} \), in an actual clinical setting in Japan, 55 patients (<50kg, \( n=44; \geq 50kg, n=11 \)) of 185 patients received >10mg/kg/d. This may be because clinicians tend to easily use the whole ganciclovir product (DENOSIN, 500mg/vial) even for patients <50kg or patients with reduced renal function, and because clinicians tend to prescribe a higher ganciclovir dose than usual to eagerly prevent immunocompromised patients from being infected with cytomegalovirus. Nevertheless, we suggest that ganciclovir should be used according to both body weight and renal function of patients, but not with the whole product content, in order to avoid drug-induced thrombocytopenia and leukopenia. From a safety perspective, ganciclovir dose should be ≤10mg/kg/d preferably and 12mg/kg/d at a maximum.

In conclusion, this study identified several factors that influenced the occurrence of ganciclovir-induced thrombocytopenia and leukopenia, and suggested that special attention should be paid to patients with these risk factors in order to avoid drug-induced thrombocytopenia and leukopenia. Further studies, particularly on the pharmacokinetic–pharmacodynamic relationship between adverse events and drug exposure, are needed to elucidate the underlying mechanism in more detail and to obtain more useful dose information.

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**Conflict of Interest** The authors declare no conflict of interest.

### Table 4. Risk Factors Identified for Ganciclovir-Induced Leukopenia by Univariate Analysis

| Risk factors | Patients with leukopenia (\( n=36 \)) | Patients without leukopenia (\( n=90 \)) | \( p \) Value |
|--------------|-------------------------------------|----------------------------------------|--------------|
| Sex (male)   | 20 (55.6%)                          | 45 (50.0%)                             | 0.57         |
| Age (mean±S.D.) | 45.9±18.6                          | 56.5±16.2                             | <0.01        |
| Cancer chemotherapy | 9 (25.0%)                           | 10 (11.1%)                            | <0.05        |
| Use of steroids | 23 (63.9%)                          | 73 (81.1%)                            | 0.99         |
| WBC count (<6000 cells/mm\(^3\)) | 24 (66.7%)                          | 34 (37.8%)                            | <0.01        |
| Creatinine clearance (<20mL/min) | 1 (2.8%)                            | 2 (2.2%)                              | 0.64         |
| Ganciclovir dose (≥12mg/kg/d) | 4 (11.1%)                           | 2 (2.2%)                              | <0.05        |
| Duration of treatment (d) | 12.8±6.2                            | 11.9±6.3                              | 0.50         |

WBC: white blood cell.

### Table 5. Risk Factors Identified for Ganciclovir-Induced Leukopenia by Multivariable Logistic Regression Analysis

| Risk factors | Odds ratio | 95% CI          | \( p \) Value |
|--------------|------------|-----------------|--------------|
| WBC count (<6000 cells/mm\(^3\)) | 3.7        | 1.6–8.7         | <0.01        |
| Ganciclovir dose (≥12mg/kg/d) | 7.8        | 1.2–49.0        | <0.05        |

WBC: white blood cell; CI: confidence interval.
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