Comparative Quantification of Chemotherapy-Induced Nausea and Emesis between the Common Terminology Criteria for Adverse Events and the Multinational Association of Supportive Care in Cancer Antiemesis Tool

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Chemotherapy-induced nausea and vomiting (CINV) are generally evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE). The Multinational Association for Supportive Care in Cancer (MASCC) developed the MASCC Antiemesis Tool (MAT) to facilitate recognition for CINV between patients and oncology specialists. In the present study, MAT and CTCAE were comparatively assessed in Japanese patients with hematological malignancies. A total of 61 patients were eligible for this study. The CTCAE data were collected from an electronic medical record system. The patients were asked to complete the Japanese version of MAT in the hospital, on the first and fourth days after the start of chemotherapy. The percentages of patients in whom nausea was completely controlled, with severity scores of zero, ranged from 70.5 to 82.0% for CTCAE and from 59.0 to 75.4% for MAT, during the first five days after the chemotherapy. The percentages of patients who had no vomiting ranged from 93.4 to 96.7% for CTCAE and from 90.2 to 98.4% for MAT. During the observation periods, the day-to-day response profiles of patients who received antiemetic treatment were comparable between CTCAE and MAT cohorts, and these two assessment tools showed good, positive correlations for nausea severity scores. The present study shows that the MAT is a useful tool for assessing the severity of CINV in patients with hematological malignancy, is comparable to CTCAE, and facilitates the identification of poor cancer care conditions by medical staff.

Key words patient self-reporting system; cancer care; chemotherapy-induced nausea and vomiting; Multinational Association for Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT); Common Terminology Criteria for Adverse Events (CTCAE)

Chemotherapy-induced nausea and vomiting (CINV) is one of the most problematic adverse events for patients with cancer,1) and its inadequate control can lead to physical disorders, including dehydration, electrolyte abnormalities, and malnourishment, which can result in the discontinuation of chemotherapy and poor of life.2,3) According to some antiemetic guidelines, the adequate management of CINV enables patients to complete chemotherapy and maintain QOL.

Adverse events, which are commonly encountered in oncology, are listed and classified by grade in the Common Terminology Criteria for Adverse Events (CTCAE), and CINV is generally assessed according to the CTCAE. Meanwhile, with improvements in supportive care, cancer chemotherapy has shifted from an inpatient to outpatient setting, and now, outpatients are required to manage side effects themselves during chemotherapy. This can inevitably lead to increased occurrences of adverse events outside the hospital; and therefore, it is important for medical staff to understand and anticipate the occurrence of side effects, including nausea and vomiting.

CINV is often classified as either acute or delayed, based on whether the CINV occurs within 24 h or more than 24 h after the start of the chemotherapy, respectively. Medical staff tend to underestimate the incidences of delayed CINV, and CINV awareness differences between patients and oncologists has become a clinical issue.5) To share the recognition of CINV between patients and oncology professionals, the Multinational Association for Supportive Care in Cancer (MASCC) developed the MASCC Antiemesis Tool (MAT) in 2004, which has been translated into more than ten languages (http://www.mascc.org/mat). The MAT is a self-reporting questionnaire that patients complete on the first and fourth days after the start of chemotherapy. Using MAT, patients record their nausea and vomiting experience and rate the level of CINV severities during the first five days after chemotherapy. The MAT has been validated in outpatients with solid tumors in the United Kingdom and United States of America,5) Japan,6) and China.7) The reports from America5) and China7) found a strong positive correlation between the Rhodes Index for Nausea, Vomiting, and Retching (INVR), as a patient’s diary, with the reliability and effectiveness of MAT records for solid tumors. The report from Japan6) showed a strong positive correlation between the patient’s diary and MAT records. However, in hematological malignancies, the usefulness of MAT has not been reported. Chemotherapy for solid tumors that focuses on QOL and chemotherapy that aims to completely cure hematological malignancies have different strengths. For this reason, we only have a limited understanding of the correlation between CTCAE and MAT with respect to the differences in evaluations between medical staffs and patients.

In the present study, we evaluated the correlation between
CTCAE and the Japanese version of MAT for outpatient CINV assessments. To our knowledge, this study is the first report on the comparison of the CINV severity scores between CTCAE and MAT for only patients with hematological malignancies.

PATIENTS AND METHODS

Patients Eligible participants were between 23 and 78 years of age and received initial standard chemotherapy treatments for Hodgkin lymphomas (HL) or non-Hodgkin lymphomas (NHL) at the Department of Hematology of the Kyushu University Hospital (June 2013 to March 2016). Patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) score greater than 2 were excluded.

Treatment Regimens The treatment regimens were as follows: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP therapy); rituximab and bendamustine (R-bendamustine therapy); and adriamycin, bleomycin, vinblastine and dacarbazine (ABVD therapy). The patients received first-course chemotherapies in inpatient hospital settings, and after the second course, outpatient chemotherapy was performed. Palonosetron was intravenously administered 30 min before the initiation of each chemotherapy. Metoclopramide, prochlorperazine, haloperidol, and/or hydroxyzine were used as rescue medications.

Data Collection and Assessment The CTCAE data were collected from an electronic medical record system. Occurrences of nausea or vomiting during overall (during 6 d after the start of chemotherapy), acute (up to 2 d), and delayed (3 to 6 d) phases were assessed. Adverse drug events (ADEs), including nausea and vomiting, were monitored during the overall study period and described in the electronic medical record system twice a day (morning and evening) by doctors, nurses, and pharmacists, according to CTCAE version 4.0.

The MAT is a patient-reported questionnaire that patients complete on the first and fourth days after the start of chemotherapy. MAT is used to assess patient nausea and vomiting experiences, based on the severity level (1 to 10; 10 = most severe) of CINV during the first five days after chemotherapy. Patients received pharmacist consent one day before or at the start of the first-course of chemotherapy. Patients were then asked to complete the Japanese version of MAT in the hospital.

This study was conducted in accordance with the Declaration of Helsinki and its amendments and received approval of the Kyushu University Graduate School and Faculty of Medicine (approval No. 24-359 of the institutional review board).

Statistical Analysis Statistical analysis was performed using JMP13 software (SAS Institute Inc. Cary, NC, U.S.A.). The relationships between CTCAE and MAT scores were analyzed using a Spearman’s rank correlation coefficient. Differences with two-tailed p values less than 0.05 were considered statistically significant.

RESULTS

Patient Baseline Clinical Characteristics A total of 61 patients with NHL or HL were eligible for this study. 39 and 17 patients with NHL received R-CHOP and R-bendamustine therapy, respectively, whereas 5 patients with HL received ABVD therapy. The patient baseline clinical characteristics are shown in Table 1.

Expression Status of Nausea and Vomiting Figure 1 shows the expression status of nausea and vomiting, using CTCAE and MAT. The percentages of patients who were completely controlled for nausea, with a score of zero, ranged from approximately 20% to 30% across the five days.
from 70.5 to 82.0% for CTCAE and from 59.0 to 75.4% for MAT, during the first five days after chemotherapy. The percentages of patients who experienced no vomiting, with a score of zero, ranged from 93.4 to 96.7% for CTCAE and from 90.2 to 98.4% for MAT. The frequencies of nausea and vomiting during the observation period tended to be higher for CTCAE than for MAT, although there was no significant difference between the assessment tools.

Fig. 2. Relationship between the Severity Scores Using CTCAE and MAT

The severity of nausea (A) and vomiting (B) during the first five days after chemotherapy was assessed by CTCAE and MAT using a scoring scale of 1 to 4 (most severe) and 1 to 10 (most severe), respectively. A score of 0 indicates no nausea or vomiting. Each column shows the number of patients who experienced nausea and vomiting on days 1–5.
As shown in Fig. 2, good positive correlations were observed between nausea severity scores using CTCAE and MAT, and the Spearman’s correlation coefficients were 0.561, 0.677, 0.726, 0.447, and 0.448 on days 1, 2, 3, 4, and 5, respectively. The correlation coefficients of the vomiting severity scores between CTCAE and MAT were 0.787, 1.000, 0.568, 0.568, and −0.024, respectively. No patient experienced CTCAE grade 3 or 4 nausea/vomiting, whereas four patients had experienced nausea with a MAT score of 8 points or more.

DISCUSSION

CINV remains a common and significant problem for patients with cancer, and is classified as either acute or delayed, based on whether the CINV occurs less than 24 h or more than 24 h after chemotherapy, respectively. Cancer chemotherapy agents that cause the worst degree of nausea and vomiting are categorized into two groups: moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC). Of the treatment regimens in the present study, R-CHOP and ABVD therapies are classified as HEC, whereas R-bendamustine therapy is classified as MEC. To control CINV, palonosetron is recommended for HEC by the Multinational Association of Supportive Care in Cancer and for MEC by the National Comprehensive Cancer Network and the American Society of Clinical Oncology. According to these antiemetic guidelines, the single administration of palonosetron is relatively effective against both acute and delayed CINV, irrespective of HEC and MEC regimens.

The severity of CINV is generally evaluated by oncology specialists using CTCAE, although this system not entirely consistent with patient evaluations, especially in the delayed phase. It was also reported that there was a perception gap between the healthcare providers and patients around experiences of nausea and vomiting (Fig. 1). It was reported that when two or three antiemetics including a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) antagonist were used according to antiemetic guidelines for MEC and HEC regimens. Meanwhile, MAT, a patient self-reporting questionnaire, has been developed by MASCC and is expected to provide a convenient and supportive tool for clinician evaluations of acute and delayed nausea and/or vomiting. A positive correlation in the severity scale between the patient diary and MAT was observed in patients with solid tumors, whereas the concordance rate between the physician assessments and patient descriptions was relatively low. To our knowledge, the present study is the first report on the comparison of the CINV severity scores between CTCAE and MAT for only patients with hematological malignancies. Our results showed that day-to-day antiemetic treatments were comparable between the CTCAE and MAT assessments during the observation periods (Fig. 1). Furthermore, the MAT assessment scores correlated well with those of CTCAE in patients who experienced delayed and acute CINV (Fig. 2). Here, 4 patients had recorded 8 points or more of a MAT score for nausea, although its grade of CTCAE was 2 or less. The difference in the severity might arise from the fact that the medical staffs lacked an understanding of the patients’ feelings or that the patients showed few signs of nausea and vomiting in front of the staffs. It was also considered that the CTCAE classification system did not entirely reflect the patient’s subjective evaluation. These findings demonstrate that MAT sufficiently allows medical staff to follow patient experiences and manage acute and delayed CINV.

The administration of cancer chemotherapeutic agents has recently shifted to hospital outpatient settings, and patients often receive outpatient chemotherapy from the first day of initiation. As a result, the medical staff might not be fully aware of the problems patients experience at home, and it may be difficult to accurately identify the emergent date and time, even when patients record their daily experiences in their own diaries. This suggests that the predicted incidences of delayed CINV are markedly underestimated, even by experienced physicians and nurses. In our present study, a good positive correlation was observed between CTCAE and MAT, although the data lacked sufficient statistical power to detect significant differences. This was partly because more than 90% of the patients had severity scores of zero in CTCAE and MAT, meaning that the CINV was completely controlled by recent advances in antiemetic management. Also, as a limitation, the chemotherapies were given in an inpatient hospital setting during the observation period, which could improve the ability of the medical staff to assess and identify periodic changes in patient conditions.

Recently, the National Cancer Institute (NCI) Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) has been developed as a new patient-reported outcome measurement system to characterize the frequency, severity, and interference of 78 symptomatic treatment toxicities (http://outcomes.cancer.gov/tools/pro-ctcae.html). PRO-CTCAE allows patients to electronically report their experiences by themselves. Basch et al. observed that overall survival was significantly associated with electronic patient-reported symptom monitoring, compared to usual care-based symptom monitoring, in the follow-up of a randomized clinical trial. However, it remains unclear whether this system is effective for managing CINV in patients with hematological malignancies. The MAT is also a patient self-reporting system, and if patients use the MAT at home and send complaints to medical staff through the web, then oncology specialists can send instruction to the patients, remotely. This would contribute to the progress of cancer care.

In conclusion, the MAT is a useful tool for assessing the severity of CINV in patients with hematological malignancy and is comparable to CTCAE. The use of MAT would facilitate the ability of medical personnel to identify poor patient conditions, even in the outpatient chemotherapy setting. We anticipate that MAT will lead to a higher QOL for patients with cancer.

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


