Treatment Strategy for Cancer-associated Venous Thromboembolism During Chemotherapy: The Keep ACT2 Concept

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Abstract. Background/Aim: The frequency of detecting cancer-associated venous thromboembolism (CAT) during chemotherapy is increasing. It is not desirable to discontinue chemotherapy for CAT. In this study, we investigated the feasibility of simultaneous progression of anticoagulant and anticancer therapy, focusing on drug interactions. Patients and Methods: We retrospectively evaluated patients with gastroenterological CAT from February 2017 to December 2020 at the Gifu University Hospital. When both chemotherapy and CAT treatments using edoxaban were performed in parallel and the thrombus disappeared, patients were defined as being Keep-ACT2 (keeping anticancer therapy and anticoagulant therapy) successful. The effect and safety of treatment strategy focusing on cytochrome P450 (CYP) metabolism using edoxaban were evaluated. Results: A total of 114 patients with CAT during chemotherapy were treated with edoxaban. Keep-ACT 2 was successful in 101 (88.6%) cases. Clinically relevant non-major bleeding was observed in 5 cases (4.4%). All 114 patients were using some drug affected by CYP metabolism, and the median number of affected cases was 5. Conclusion: Combined use of edoxaban for CAT may lead to sustainable therapy for gastroenterological cancer patients who are administered several drugs.

There will be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 (1). Although avoidance of factors that may cause cancer as well rate of cancer screening has been improving, the number of cancer patients is increasing each year (2). Besides, cancer management including surgery or chemo-radiotherapy are being implemented all over the world, complete cure is still difficult (3). Meanwhile, efforts related to prevention and risk classification of perioperative venous thromboembolism have been reported (4, 5). In recent years, the onset of venous thrombus during systemic chemotherapy has become a hot topic. Among outpatients receiving chemotherapy, cancer-associated thromboembolism (CAT) was the second leading cause of death (6).

We aimed to better understand this condition and take measures so that patients can continue to receive cancer treatment. Because cancer patients are elderly and are naturally receiving a variety of medications, the intensity of drug interactions can be particularly high. Therefore, this study focuses on the measures needed to continue chemotherapy and combat CAT, taking into account drug interactions.

Patients and Methods

The direct oral anticoagulant (DOAC) edoxaban (Daiichi Sankyo Co., Ltd., Tokyo, Japan) was used for CAT therapy. D-dimer measurement was required at the first visit and when the chemotherapy regimen was changed. If the D-dimer value was 1.2 μg/ml or more, lower extremity vein sonography was conducted. Edoxaban was used in all patients with CAT found in our department from February 2017 to December 2020. We retrospectively gathered the records of gastroenterological cancer patients who were found to have CAT and were treated by chemotherapy and edoxaban in combination.

We investigated the rate of thrombus disappearance and bleeding events. When both cancer treatment and CAT treatment using edoxaban were performed in parallel and the thrombus disappeared, patients were defined as being Keep-ACT2 (Keeping anticancer therapy and anticoagulant therapy) successful. When the thrombus
Table I. Background of 114 patients with CAT treated with edoxaban plus chemotherapy over 4 years.

<table>
<thead>
<tr>
<th>Underlying diseases, n (%)</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Hyperlipidemia +/-</td>
<td>47 (41.2%)/67 (58.8%)</td>
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<tr>
<td>Diabetes mellitus +/-</td>
<td>22 (19.3%)/92 (80.7%)</td>
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<tr>
<td>Hypertension +/-</td>
<td>60 (52.6%)/54 (47.3%)</td>
</tr>
<tr>
<td>Hyperuricemia +/-</td>
<td>15 (13.2%)/99 (86.8%)</td>
</tr>
<tr>
<td>Heart failure +/-</td>
<td>9 (7.9%)/105 (92.1%)</td>
</tr>
<tr>
<td>Stroke +/-</td>
<td>13 (11.4%)/101 (88.6%)</td>
</tr>
<tr>
<td>Arrhythmia +/-</td>
<td>15 (13.2%)/99 (86.8%)</td>
</tr>
</tbody>
</table>

CAT: Cancer-associated thrombosis; SD: standard deviation; n: number.

Results

From February 2017 to December 2020, 117 cases of CAT treated with edoxaban were monitored in patients with gastrointestinal cancer. Excluding 3 cases in which edoxaban was used for postoperative venous thromboembolism (VTE), the remaining 114 cases of CAT occurred during chemotherapy. The mean age of these patients with CAT/Total cases over 4 years by cancer type [% (95% confidence interval)]

- Esophageal cancer: 19/182 [10.4 (6.4-15.6)]
- Gastric cancer: 20/450 [4.4 (2.7-6.8)]
- Colorectal cancer: 39/720 [5.4 (3.9-7.3)]
- Hepatocellular cancer: 4/110 [3.6 (1.0-9.1)]
- Pancreatic cancer: 26/257 [10.1 (6.7-14.4)]
- Gall bladder and bile duct cancer: 6/66 [9.0 (3.4-18.7)]
- Other: 0/3 [0.0 (0.0-0.7)]

**Statistical analysis.** Results were expressed as the median (interquartile range) or mean (standard deviation) for quantitative variables and percentage for qualitative variables. The \( \chi^2 \) test or Fisher’s exact test was used for categorical variables, and the nonparametric Wilcoxon rank sum test was used for continuous variables. A \( p \)-value <0.05 was considered significant. All statistical analyses were performed with the SPSS 27.0 software package (SPSS).

**Ethical approval and consent to participate.** This study was conducted in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Ethics Committee of Gifu University School of Medicine (IRB Numbers: 2019-173). Written informed consent for this study was obtained from all patients.

Figure 1. Transition of D-dimer. Values are mean±SD. The D-dimer value before treatment was 17.1±15.9 μg/ml and 2.6±6.7 μg/ml after treatment (\( p<0.001 \)). SD: Standard deviation.
patients [67 men (58.8%), 47 women (41.2%)] was 71.8±9.4 years, and their mean body weight was 53.6±12.5 kg (Table I). Esophageal cancer tended to be the more commonly treated in our Department during this period. Pulmonary thromboembolism (PTE) occurred in 29 patients (25.4%) and deep vein thrombosis (DVT) in 113 patients (99.1%). In one patient (0.8%), PTE was present but no DVT was observed. The D-dimer value before treatment was 17.1±15.9 μg/ml and 2.6±6.7 μg/ml after treatment ($p<0.001$) (Figure 1).

Among all patients with any kind of cancer, Keep-ACT 2 was successful in 101 (88.6%) and unsuccessful in 13 (11.4%) patients (Figure 2). Among these 13 patients, the extent of DVT did not change in one patient. The cancer continued to worsen, and the extent of VTE decreased in one patient. The extent of DVT decreased and the D-dimer level normalized, but organized DVT remained. 6 cases

- The extent of DVT did not change. 1 case
- The cancer continued to worsen and the extent of VTE decreased. 1 case
- The extent of DVT decreased and D-dimer level normalized, but organized DVT remained. 6 cases
- VTE worsened at the terminal stage and bleeding occurred from the tumor. 1 case
- Cancer progressed and DVT disappeared but Trousseau syndrome developed. 2 cases
- Both D-dimer and thrombus volume tended to decrease, but the patient died of cancer in the terminal stage. 2 cases

Both the D-dimer value and thrombus volume tended to decrease in 2 patients, but they both died of cancer in the terminal stage. Cancer stages of the Keep-ACT 2 successful patients were stage I in 6, II in 20, III in 27, and IV in 48 patients, and that in all 13 Keep-ACT 2 unsuccessful patients was stage IV ($p<0.001$), with gastric cancer in 4, gall bladder and bile duct cancer in 3, pancreatic cancer in 4, and colorectal cancer in 2.

In terms of safety of using edoxaban during chemotherapy, local bleeding from gastric cancer and bile duct cancer occurred in 2 patients. One patient with colon cancer experienced epistaxis with the addition of the adverse event of thrombocytopenia caused by chemotherapy. Subcutaneous bleeding at the thoracotomy wound for EC occurred 2 months after surgery in one patient. These occurrences were within the acceptable range of clinically relevant non-major bleeding.

According to the specified dose reduction criteria for edoxaban, the dose was 30 mg/day in 82 patients (71.9%), 60 mg/day in 31 patients (27.2%), and 15 mg/day in 1 patient (0.9%). The median number of months of edoxaban use was 6 months, and the maximum was 31 months. Examination of the number of drugs affected by CYP metabolism during chemotherapy in the 114 patients revealed that all 114 were using some, and the median number of drugs taken was 5. Up to 11 drugs affected by CYP metabolism were being used (Figure 3).
To the best of our knowledge, this is the first study to evaluate the completion rate and risk of CAT treatment and ongoing chemotherapy by focusing on CYP metabolism. One in two people will develop cancer, and thrombosis has become the second leading cause of cancer-related death (6). Cancer was ranked first as the cause of VTE in the report of the Japan VTE Treatment Registry (8). In 2017, the International Society on Thrombosis and Haemostasis (ISTH) suggested the importance of the coexistence of malignant tumors in patients with VTE whose etiology is not clear (9).

Throughout the treatment of cancer, it makes sense to perform early D-dimer measurements and lower limb sonography at the bedside in the event of CAT. The D-dimer level should also be checked when the chemotherapy regimen changes (10). In our Department, the frequency of D-dimer measurement is increasing, as is the yearly number of sonographic examinations of the lower extremity veins. As well, many incidences of asymptomatic PTE are accidentally found by diagnostic imaging during chemotherapy.

Anticancer agents and their associated adverse events such as dehydration from loss of appetite and diarrhea, catheter placement, decreased activity of daily life, and molecular-targeted agents can cause the occurrence of CAT (11). Cancer itself has a molecular pathological predisposition that triggers thrombus (12). An appropriate strategy against CAT may allow the prolongation of cancer treatment. Nowadays, cancer treatment is wide-ranging, and surgery is no longer the only means of treatment. Anticancer drugs, immune checkpoint inhibitors, and supportive care continue to diversify.

We promoted the concept of Keep-ACT² that maintains both anticancer therapy and anticoagulant therapy by ensuring that interaction between the drugs used in both treatments is low. In recent years, evidence comparing DOACs with low-molecular-weight heparin for CAT patients has been reported, and the use of DOACs in CAT treatment is increasing (13-15). Most of the enzymes involved in drug metabolism are reported to be CYP (16). Actually, some anticancer drugs, steroids, antiemetics, antibacterial agents, and proton pump inhibitors used as supportive care drugs undergo CYP metabolism. In addition, cancer patients are generally middle-aged and often have underlying illnesses and are receiving various drug therapies, so the strength of drug interactions may be particularly enhanced in these patients (17).
In fact, anticancer drugs and hormone therapy drugs that affect the blood concentration of the DOAC itself have been reported (18). Among the DOACs, CYP3A4 metabolism of edoxaban is less than 10%. In addition, all DOACs are substrates for P-glycoprotein and are said to be affected by P-glycoprotein inhibitors/inducers (19-27). Thus, the combined use of P-glycoprotein inhibitors/inducers and CYP3A4 inhibitors/inducers should be avoided, especially in cancer patients when using other DOACs (25). We found that patients with CAT were taking about 5 concomitant medications affected by CYP metabolism in this study. The incidence of CAT in the present study tended to be high in patients with esophageal cancer. Among the 19 patients continuing chemotherapy for esophageal cancer who were treated for CAT with edoxaban, the thrombus disappeared in all 19 and chemotherapy was not discontinued. In esophageal cancer, there may be an effect from not using molecular-targeted drugs that affects angiogenesis, and even if CAT was found, it was possible to carry out anticancer and anticoagulant drug therapy in parallel, and furthermore, the thrombosis disappeared. In fact, among 1,788 cases of gastroenterological cancer treated in our Department during the same period, 114 (6.4%) cases were diagnosed as having CAT. This percentage was very similar to a previously reported percentage (28). Considering the overall success rate of Keep-ACT and low rate of bleeding events in this study, our findings indicate that edoxaban is a DOAC that may allow CAT treatment to be performed in parallel with chemotherapy safely. Heparin is used as needed after appropriate judgment of the risk thrombosis of massive versus non-massive scale, but in this study, heparin was not administered in any patients. Because we are trying to detect VTE earlier by routinely performing D-dimer measurements and lower extremity vein echography, there were no cases of massive thrombosis requiring prior use of heparin for VTE. However, in Stage IV patients, how long a DOAC should be used as treatment for CAT may be controversial.

Results may be limited due to the small number of cases examined this time and the non-prospective comparison with other anticoagulants. It is also necessary to limit the targeting cancer and prospectively consider more adverse events to confirm drug interactions in the future.

Conclusion

Considering ways to eliminate the factors like CAT that prevent continuation of treatment may lead to sustainable treatment strategies for gastroenterological cancer patients who are administered several drugs. The rate of occurrence of CAT in the studied patients was not low, and the combined use of anticoagulant therapy considering drug interaction with edoxaban during chemotherapy appeared to be feasible.

Conflicts of Interest

Dr. Yoshida reports grants, personal fees, and non-financial support from EA Pharma Co., Ltd., Sanofi, Yakult Honsha Co., Ltd., Chugai Pharma Co., Ltd., Taiho Pharma Co., Ltd., Takeda Pharma Co., Ltd., Eli Lilly Japan K.K., Daiichi Sankyo Co., Ltd., Ono Pharma Co., Ltd., Merck Serono Co., Ltd., and Novartis Pharma K.K., and grants from Kyowa Hakko Kirin Co., Ltd. outside the submitted work.

Authors’ Contributions

Contributions to conception and design of the study and performed data analysis and interpretation: Tanaka Y, Sato Y, Suet sugi T, Mase J, Takara R, Okumura N, Matsuhashi N. Performed data acquisition and provided administrative and technical support: Takahashi T, Yoshida K.

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