博士論文（要約）

A randomized controlled study evaluating the efficacy of NK1 receptor antagonist for moderately/highly emetogenic chemotherapies in hematological malignancies.

（血液内科領域の中等度・高度催吐性化学療法におけるNK1受容体拮抗薬の使用方法の研究）

氏　　名　　那須　涼

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect among cancer patients. The emetogenicity of chemotherapeutic agents is graded according to the expected rate of emesis without effective antiemetic prophylaxis; over 90 % of patients receiving highly emetogenic chemotherapy (HEC) and 30% to 90% receiving moderately emetogenic chemotherapy (MEC) would experience emesis. The occurrence of CINV is typically biphasic; thus, recommendations for antiemetic therapy are targeted to prevent CINV in the acute phase, occurring in the first 24 hours, or in the delayed phase, occurring later. Although 5-hydroxytryptamine receptor antagonists (5HT3-RAs) have significantly improved patients' quality of life by preventing acute phase of CINV, these agents alone are insufficient in preventing CINV in the delayed phase even when administrated with corticosteroids.

The novel neurokinin-1 (NK-1) receptor antagonist, aprepitant, is the first anti-emetics that prevent both acute and delayed CINV by blocking substance P in central nervous system. The efficacy of aprepitant, combined with 5HT3-RAs and dexamethasone, has been extensively studied and established in cisplatin-based regimen for malignant solid tumors. Accordingly, combination of 5HT3-RAs, corticosteroids, and NK-1 antagonists has become standard of care for patients receiving HEC.

The chemotherapeutic regimens for hematological malignancies have distinct features from those for solid malignancies. Firstly, chemotherapy regimens for hematological malignancies have much higher dose intensity comprising of multiple drugs and spanning for several days. Thus, it remains unclear whether the ordinal usage of aprepitant (125 mg on day 1 and 80 mg on day 2-5) is sufficient for the longstanding chemotherapies applied for hematological malignancies. Secondly, steroids are frequently included in hematological regimens in anticipation of antitumor effect, especially for lymphoid malignancies, and this makes it difficult for hematologists to use dexamethasone in anti-emetic protocols. Therefore, the effectiveness of aprepitant to prevent CINV in the settings without dexamethasone use should be assessed. Until now, several studies have demonstrated the benefit of incorporating aprepitant in antiemetic regimens for conditioning regimens for hematopoietic stem cell transplantation. However, little evidence was shown for aprepitant administration as antiemetic prophylaxis in conventional chemotherapies for hematological malignancies. To address these issues, I conducted a randomized controlled study to evaluate the efficacy of aprepitant in patients receiving chemotherapeutic agents for hematological malignancies.

In this study, the patients who received conventional anti-emetic therapies were randomly allocated to either aprepitant or control groups. The aprepitant group received aprepitant for the first 5 days of treatments combined with 5HT3-RAs, and the control group received only 5HT3-RAs. Steroid was not included in the CINV prophylaxis unless included in the chemotherapeutic protocols. Comparing these two arms, I examined the efficacy of aprepitant in prevention of CINV for hematological chemotherapies.

The primary endpoint of this study was the overall complete response (CR), which was defined as no emetic episodes or no administration of rescue medications during the first 10 days after the start of chemotherapies. Secondary endpoints were the rate of (1) no emesis, (2) no rescue medications, and (3) no significant nausea during the 10-day observation. Degree of nausea was measured daily with visual analog scale (VAS). Furthermore, actual oral intake, which has rarely been evaluated in the previous anti-emetics' studies, was assessed by patients' self-evaluation.

Forty nine patients were enrolled in and 41 (22 patients in the aprepitant arm and 19 in the control arm) of them completed the study. There was no withdrawal due to the side effect of aprepitant.

The overall CR was significantly better with aprepitant use. CR rate was 82% in the aprepitant arm and 47% in the control arm (p=0.026). Although there was no significant difference in CR rates in the acute phase (p=0.47), CR rate in the late phase tended to be more favorable in the aprepitant arm compared to the control arm (82% versus 58%, p=0.17). Emetic episodes during the overall observation period occurred less frequently in the aprepitant arm than in the control arm (9% versus 42%, p=0.026). This result indicates that aprepitant suppressed emesis almost completely. In contrast, aprepitant did not reduce salvage anti-emetics use (p=0.47), nor level of nausea quantified by VAS. The self-reported oral intake revealed that almost 50% of the patients with aprepitant use maintained usual amounts of oral feeding throughout the observation period, whereas this rate dropped significantly to about 21% at day 6 among patients without aprepitant use. (p=0.049).

With univariate analysis, underlying diseases (composed of "acute leukemia", "malignant lymphoma", and "multiple myeloma"; p=0.020) and chemotherapies (composed of "induction or consolidation for acute leukemia", "platinum-based therapy", and "auto HSCT conditioning regimen"; p=0.024) significantly affected CR rate. I conducted a multivariate analysis including the factor "use of aprepitant" fixed. Although none of the factors were significant, conditioning regimens for autologous transplantation were sub-significantly associated with a decreased response rate. In order to explore the traits that would potentially favor aprepitant use, I conducted sub-group analyses. Patients receiving chemotherapies for acute leukemia had little benefit from aprepitant (odds ratio (OR) = 0.74: 95% confidential interval (CI) = 0.03-29.4, p=1.0).

Aprepitant succeeded in preventing vomiting in the overall period without severe side effects in our study. Although not statistically significant, patients with aprepitant use tend to have much more merit in the delayed phase than in the acute phase. Based on the fact that substance P is a major cause of CINV in the delayed phase, these findings are concordant with the mechanism of action of aprepitant, which selectively blocks binding of substance P to NK1 receptors of vomiting centers in the central nervous system.

Among the various treatments included in this study, our results indicate that the additional effect of aprepitant was more prominent in the steroid containing regimens than in the steroid non-containing ones. This result can be partly explained by the difference in basal emetogenicity

among the regimens. Concretely, higher CR rate was observed among the patients treated with steroid non-containing therapies compared to those with steroid containing (67% versus 38%) in the control arm. Steroid non-containing regimens mostly consisted of anthracycline and/or cytarabine-based chemotherapies for acute leukemia. This group of patients is recognized to have little merit from aprepitant administration.

In the aprepitant arm, none of the patients who underwent autologous transplantation achieved CR and detailed analysis of this group indicated that all of the subjects suffered from late phase CINV. Thus, current strategy of aprepitant is not sufficient to control CINV for this group.

In contrast to marked difference of emetic episodes between the two arms, aprepitant had little impact on preventing nausea. Similar results were also observed in other trials that assessed efficacy of aprepitant use in chemotherapies for solid tumors. Despite the fact that precise assessment is difficult, nausea should be controlled as well as emesis because it significantly impairs patients' quality of life and motivation to receive further chemotherapies. It is interesting to note that olanzapine, an antipsychotic agent blocks multiple transmitters including dopamine, serotonin, and adrenergic receptors, is much more effective to control nausea in the delayed phase than aprepitant. It is not clarified whether the difference of target neurotransmitters can explain the different effect of aprepitant and olanzapine on nausea control.

Daily oral food intake was self-assessed in this study. About 50% of the patients in the aprepitant arm maintained usual amounts of oral feeding throughout the observation period whereas this rate dropped significantly and only 21% had normal food intake in the control arm at day 6. However, generalized estimating equation analysis did not identify aprepitant as the significant factor for all observational period (pre-therapy oral intake impairment: $\beta=39.1$, $p<0.001$. aprepitant arm: $\beta=0.107$, $p=0.78$). Furthermore, I examined whether steroid-containing regimens had any effect on appetite, however, and found that this was not a significant factor to influence appetite ($\beta=-0.662$, $p=0.16$). Instead, degree of appetite loss was closely associated with nausea scale (p-value = 2.2x10-16, spearman's rank test).

The known adverse effects of aprepitant are hiccups, asthenia, and diarrhea, and rare but serious events include neutropenia. In this study, no patients experienced severe adverse events that were attributable to aprepitant. The safety profile highlights the merit of incorporating aprepitant in the anti-CINV prophylaxis.

In conclusion, this is the first study to investigate the advantage of adding aprepitant to conventional 5HT3-RAs-based CINV prophylaxis in moderately/highly emetogenic chemotherapies for hematological malignancies. As I obtained sufficient anti-emetic effect without obvious adverse events, additional aprepitant use is recommendable. Further elucidation is required to establish the standard CINV prophylaxis for each chemotherapy regimen based on its individual efficacy profile.