Chemotherapy-induced nausea and vomiting (CINV) is a common complication of cancer chemotherapy that can severely affect patients' quality of life (QoL) [1]. In general, CINV is classified into acute CINV which occurs within 24 h of chemotherapy and delayed CINV, which occurs 24 h and up to 5 days after chemotherapy administration [2]. Other important subtypes are anticipatory, breakthrough, and refractory emesis [3].

Multiple clinical studies have shown that patient characteristics can predict those who are at higher risk in developing CINV [4-6]. The incidence of CINV in chemonaive patients is up to 20% in patients without risk factors and 76% in those with risk factors [7]. At present, the identified risk factors include young age, female gender, minimal alcohol intake, history of motion sickness, history of morning sickness during pregnancy, and prior adverse experience with chemotherapy [8].

The standard treatment for breast cancer involves the use of chemotherapy [9]. However, combination chemotherapy regimens are associated with better response rates compared to single-agent therapies. However, it is associated with CINV, a serious adverse effect that is able to negatively impact on patients' QoL and also patients' compliance [10-12].

Multiple practice-based guidelines are recommending the use of antiemetic drugs against CINV [13-15].

National Comprehensive Cancer Network (NCCN) guidelines provide a classification that addresses the likelihood of CINV that is primarily related to the emetogenic potential of the specific chemotherapeutic drugs. Anthracycline-based chemotherapy is a highly emetogenic chemotherapy (HEC) [16]. Thus, chemotherapy drugs can be categorized as highly emetogenic (>90% frequency of emesis, for example, combination of anthracycline and cyclophosphamide (AC), cisplatin and cyclophosphamide >1500 mg/m²), moderately emetogenic (30%-90% frequency of emesis, for example, carboplatin, cyclophosphamide ≤1500 mg/m², daunorubicin, doxorubicin, epirubicin, and ifosfamide), low emetogenic (<10% frequency of emesis, for example, cytarabine 100–200 mg/m², docetaxel, etoposide, S-fluorouracil, gemcitabine, and paclitaxel), and minimal emetogenic (<10% frequency of emesis, for example, bleomycin, vinblastine, vincristine, and vinorelbine). The frequencies are in the absence of effective antiemetic prophylaxis [17-21].

Multinational Association of Supportive Care in Cancer (Eurasian Society for Medical Oncology (MASCC/ESMO) antiemetic guidelines [22,23] recommend prophylaxis with a 5-hydroxytryptamine-3 receptor antagonist (5-HT₃RA) and dexamethasone for patients treated with moderately emetogenic chemotherapy (MEC) other than carboplatin-based regimens. However, for the prevention of CINV associated with HEC (including AC) and carboplatin based regimens, the triple combination of a 5-HT₃RA, a neurokinin-1 receptor antagonist (NK₁RA), and dexamethasone is advised, along with addition of olanzapine to the triplet when occurrence of nausea is an issue. Similar recommendations have been issued by the NCCN [24] and the American Society of Clinical Oncology [17] for CINV prophylaxis in the HEC and MEC settings. Recently, additional formulations of NK₁RAs that increase the convenience of administration of antiemetics have been developed and approved in the U.S. In 2018, for example, intravenous (IV) NEPA (fixed combination of fosnetupitant and palonosetron) [25], aprepitant emulsion for injection [26], and rolapitant injectable emulsion [27,28]; IV NEPA also recently received approval in Europe [29]. After the occurrence of anaphylaxis, anaphylactic shock, and hypersensitivity reactions in the clinic with rolapitant injectable
emulsion, a safety warning was issued [30] that led to the suspension of its distribution [31]. The new IV formulations of NEPA and aprepitant have recently been incorporated in the NCCN antiemetic guidelines and are recommended for the HEC and MEC settings [24]. Moreover, IV NEPA is advised as an alternative to oral NEPA in the HEC (AC) and carboplatin settings by MASCC/ESMO [22,23].

The prevention is the main goal of international antiemetic guidelines. Correct management of nausea and vomiting in the first chemotherapy cycle is critical as CINV occurrence during first administration of emetogenic chemotherapy can lead to increased CINV risk in subsequent cycles [32,33]. Hence, it is advisable to adhere by the guideline-consistent usage of antiemetic regimens for good compliance to the chemotherapy with cancer [34-36]. Conversely, non-adherence to antiemetic guidelines lead to suboptimal CINV control [36]. However, several studies have reported low guideline adherence for patients receiving HEC and MEC both in Europe [36-38] and the U.S. [39].

The present research aims to study about the prescription pattern of prophylactic antiemetics in breast cancer patients receiving chemotherapy in a tertiary care hospital in Assam.

MATERIALS AND METHODS

Objective
The aim of the study was to study the prescription pattern of prophylactic antiemetics in breast cancer patients.

Methods
The study was done at State Cancer Institute, Gauhati Medical College, Guwahati. It was a retrospective observational study. The study was carried out for a period of 3 months. It included 103 breast cancer patients undergoing chemotherapy who were prescribed with antiemetics. A suitable data collection form was used to collect data. The data were transferred to Microsoft Excel 2010 and descriptive statistics such as frequency and percentage were calculated. The Institutional Ethics Committee permission was obtained from Gauhati Medical College and Hospital to carry out this study.

Inclusion criteria includes
The following criteria were included in the study:
- Patients 18 years of age or older with breast cancer who were scheduled to receive chemotherapy regimen
- Patients who are prescribed with antiemetics during chemotherapy.

Exclusion criteria includes
The following criteria were excluded from the study:
- Patients who do not receive any antiemetics
- Patients with incomplete prescription information.

RESULTS
In this study, we enrolled 103 breast cancer patients who fulfilled the inclusion criteria. Among 103 breast cancer patients, majority 102 (99.03%) were found to be female patients and only 1 (0.97%) was a male patient who underwent chemotherapy with antiemetics (Fig. 1).

Among the recruited patients, majority of patients were in the age group of 40–49 years (32, 31.07%), followed by 50–59 years (26, 25.24%), and the mean age was found to be 49±11.16 years (Fig 2).

Again when we recorded their medical history, we found that majority of them did not suffer from any other comorbidities, that is, 96 (93.21%) out of 103 patients and rest were either hypertensive 2 (1.94%) or diabetic 2 (1.94%) or both hypertensive and diabetic 2 (1.94%) and only 1 (0.97%) patient was hypothyroid (Fig. 3).

In this study, we had recruited 103 breast cancer patients receiving chemotherapy, along with prophylactic antiemetic agents. We had analyzed 141 prescriptions and found that the same patient received more than one regimen of chemotherapy agents. Prophylactic antiemetic therapy was also analyzed using the standard international guidelines, that is, NCCN.

When we classify the chemotherapeutic regimens according to the level of their emetogenic risk using NCCN guidelines, 72 (51.06%) chemotherapy regimen were with high emetogenic potential, 3 (2.13%) regimen with moderate emetogenic potential, 61 (43.26%) regimen with low emetogenic potential, and 5 (3.55%) regimen with minimal emetogenic potential (Table 1).

In this study, it was seen that most commonly prescribed anticancer agent was paclitaxel (49, 34.75%) followed by anthracycline +
cyclophosphamide (AC) combination (47, 33.33%). AC combination was the most frequently used chemotherapeutic regimen in the HEC group, epirubicin + cyclophosphamide regimen in the MEC group, paclitaxel in the LEC, and pertuzumab + trastuzumab regimen in the minimal emetic risk group (Table 2).

Appropriate antiemetic drugs were prescribed to 58 (80.56), 2 (66.67), 2 (3.28) of HEC, MEC, and LEC regimen, respectively. Fourteen (19.44) of HEC, 1 (33.33) of MEC, and 59 (96.72) of LEC regimen were prescribed with antiemetic therapy which did not follow NCCN guidelines (Table 3).

Patients receiving minimal emetogenic potential chemotherapy without antiemetic therapy as per guideline were not included in our study. Five patients who were receiving antiemetic prophylaxis (inappropriate as per NCCN guidelines) were included in our study (Table 4). About 43.97% of the antiemetic regimen were found following NCCN guidelines.

DISCUSSION
Evidence-based recommendations for CINV have been developed during the past few decades. Many international guidelines have been in use for prevention of CINV.

The present study was conducted to evaluate the prescription pattern of prophylactic antiemetics in breast cancer patients. In our study, most common age group was 40–49 years (31.07%). Shah et al. studied drug utilization pattern and found highest breast cancer in similar age group [40].

Most frequently prescribed regimen was paclitaxel 49 (34.75%) followed by AC regimen (anthracycline + cyclophosphamide combination) 47 (33.33%). AC regimen was one of the most common regimens for the treatment of breast cancer in similar studies [40-43].

In high emetogenic potential anticancer agents, three regimens were used. AC regimen was prescribed to 47 (65.28%) of 72, carboplatin-based regimen was prescribed to 17 (23.61%) of 72 patients, and 5-fluorouracil + epirubicin + cyclophosphamide was prescribed to 8 (11.11%) patients. Fifty-eight (80.56%) of 72 prophylactic antiemetic prescriptions were appropriate as per recommendation of NCCN guidelines 2022 [15]. It consists of combination of three drugs, one from NK1 RA (aprepitant, netupitant, and fosaprepitant), one from 5-HT3 RA (ondansetron and palonosetron), and dexamethasone. In all 58 (100%) prescriptions, dexamethasone was prescribed and other drugs were 28 (48.28%) fixed combination of netupitant 300 mg/palonosetron 0.5 mg, 25 (43.10%) ondansetron, 5 (8.62%) palonosetron, 17 (29.31%) aprepitant, and 13 (22.41%) fosaprepitant, respectively.

Five (6.94%) of 72 prescriptions were over antiemetic prophylaxis where two 5-HT3 RA were prescribed. Nine (12.5%) of 72 prescription were under antiemetic prophylaxis as dexamethasone was not prescribed and 5HT3RA was not included in one of them. Here, 80.56% of antiemetic prophylaxis was in consistent with NCCN guidelines. Guidelines consistency was highest for patients receiving high emetogenic potential anticancer agents.

In moderate emetogenic anticancer agents, 3 (100%) patients received Epirubicin+Cyclophosphamide. Antiemetic prophylaxis used in this group was consistent with NCCN guidelines in 66.67% prescriptions.

In low emetogenic anticancer agents, paclitaxel (49 [80.33%] of 61) was the most frequently prescribed chemotherapeutic agent followed by docetaxel (10 [16.39%] of 61). Two (3.28%) prescriptions were optimal regarding prophylactic antiemetic. In 55 (90.16%) of 61 LEC prescriptions, both serotonin receptor antagonist and dexamethasone were prescribed. Paclitaxel and docetaxel can produce hypersensitivity reaction as supported by many studies and use of dexamethasone in these treatment groups may be as a preventive measure against it [44]. In a similar single-center study, adherence to guidelines in the prescription of antiemetic prophylaxis in low emetogenic anticancer agent was only 11%, because rest of the patients received 5-HT3 RA in addition to corticosteroids [39].

In minimal emetogenic anticancer agents, most frequently prescribed regimen was pertuzumab and trastuzumab 4 (80%) followed by trastuzumab 1 (20%) of five prescriptions. The antiemetic prophylaxis prescribed with these regimens was not supported by NCCN guidelines.

The reasons of guidelines inconsistency varied across emetogenic risk group.

A study by Ayako Okuyama, found a substantial number of patients receiving chemotherapy with minimal or low emetic risk, were prescribed prophylactic antiemetics drugs [45].

CONCLUSION
Studies are needed to explore barriers of appropriate implementation of antiemetic guidelines. Education, training of all individuals involved in chemotherapy is needed to improve guidelines adherence. Institutional antiemetic guideline can be developed for better assessment and management of CINV.

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Table 4: Pattern of antiemetic regimen used for chemotherapy regimen with different emetogenic potential

<table>
<thead>
<tr>
<th>Emetogenic potential</th>
<th>Antiemetic agents used and number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly emetogenic chemotherapy</td>
<td>Combination of netupitant 300 mg/palonosetron 0.5 mg+dexamethasone (28)</td>
</tr>
<tr>
<td>Number of patients (72)</td>
<td>Ondansetron+aaprepitant+dexamethasone (12)</td>
</tr>
<tr>
<td>NCCN recommendations</td>
<td>Ondansetron+fosaprepitant+dexamethasone (13)</td>
</tr>
<tr>
<td>NK1RA+5HT3RA+dexamethasone</td>
<td>Palonosetron+aaprepitant+dexamethasone (5)</td>
</tr>
<tr>
<td>Moderately emetogenic chemotherapy</td>
<td>Combination of netupitant 300 mg/palonosetron 0.5 mg+dexamethasone (5)</td>
</tr>
<tr>
<td>Number of patients (3)</td>
<td>Ondansetron+fosaprepitant (2)</td>
</tr>
<tr>
<td>NCCN recommendations</td>
<td>Aprepitant (1)</td>
</tr>
<tr>
<td>5HT3RA+dexamethasone+NK1RA</td>
<td>Combination of netupitant 300 mg/palonosetron 0.5 mg (1)</td>
</tr>
<tr>
<td>Low emetogenic chemotherapy</td>
<td>Combination of netupitant 300 mg/palonosetron 0.5 mg+dexamethasone (1)</td>
</tr>
<tr>
<td>Number of patients (61)</td>
<td>Ondansetron (2)</td>
</tr>
<tr>
<td>NCCN recommendations</td>
<td>Aprepitant+ondansetron+dexamethasone (1)</td>
</tr>
<tr>
<td>Dexamethasone or metoclopramide or prochlorperazine or 5HT3RA</td>
<td>Fixed dose combination of netupitant 300 mg/palonosetron 0.5 mg (3)</td>
</tr>
<tr>
<td>Minimal emetogenic chemotherapy</td>
<td>Palonosetron+dexamethasone (7)</td>
</tr>
<tr>
<td>Number of patients (5)</td>
<td>Ondansetron+fosaprepitant+dexamethasone (2)</td>
</tr>
<tr>
<td>NCCN recommendations</td>
<td>Ondansetron+fosaprepitant (1)</td>
</tr>
<tr>
<td>No routine prophylaxis</td>
<td>Combination of netupitant 300 mg/palonosetron 0.5 mg (5)</td>
</tr>
<tr>
<td></td>
<td>Ondansetron+fixed dose combination of netupitant 300 mg/palonosetron 0.5 mg+mg+dexamethasone (1)</td>
</tr>
<tr>
<td></td>
<td>Combination of netupitant 300 mg/palonosetron 0.5 mg+mg+dexamethasone (1)</td>
</tr>
</tbody>
</table>

NCCN: National Comprehensive Cancer Network, NK1RA: Neurokinin-1 receptor antagonist

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CONFLICTS OF INTEREST
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