Chapter

Evaluation of the Medication Safety of Chemotherapy Drugs

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Abstract

To evaluate the medication safety of chemotherapy drugs at a tertiary care hospital, with complete reporting of prescription errors, classifying prescription errors, complete detailing of watched medication administration errors (MAEs) by nurses, ordering watched MAEs, and figuring improvement methodologies. Likewise, in relation to side effects, how to overcome side effects, which antiemetic treatments to use, how to survey the appropriateness of requesting and apportioning. An imminent, observational, non-interventional contemplate study was driven at the Oncology Department, Baptist Hospital, Bangalore for half a year. All the data was collected from patient medical records according to case record structure. An aggregate of 70 patients tolerating chemotherapy were observed for information on a sort of side effects, prescription missteps and other relevant information like demographic findings, treatments, and drugs used to manage the adverse effects (AEs) collected from the patient's medical records. The data was characterized reliant on various parameters. The watched side effects according to different organ frameworks were orchestrated and appeared differently in relation to the distributed writing and bundle embeds. Among the 70 patients, 22 (31.4%) were males and 48 (68.57%) were females. Moreover, the age interval within these two groups was of 20–65. From the 70 patients, the number of chemotherapy cycles was of one for 14 (20%) patients, two for 16 (22.85%), three for 16 (22.85%), four for 5 (7.14%), five for 6 (8.57%), six for 9 (12.85%), and more than six for 4 (5.71%) patients, mostly due to maintenance chemotherapy. The evaluation of our information uncovered that the cancer with the most elevated predominance was breast cancer (24.28%), pursued by blood and bone marrow cancer (5.71%) in females, whereas in males were blood and bone marrow (4.28%), followed by lung cancer (2.85%), non-Hodgkin lymphoma (2.85%), and colon cancer (2.85%). The present study demonstrated that in both gender groups, the most influenced organ framework was gastro intestinal tract (GIT), trailed by skin and subcutaneous tissue, musculoskeletal, blood and nervous system. The most prescribed antiemetic drug was ondansetron (81.42%), and the normally endorsed chemotherapy agents in our setting were shown to be cisplatin (21.42%), carboplatin (17.14%), and paclitaxel (14.28%). The total percentage of errors on the 70 prescriptions was 24.28. Most of the errors were due to drug–drug interactions (10%). The total percentage of errors in drug administration performed by nurses was found to be 11.42%, out of which in 2.85% of the cases, it was used the wrong drug dose. The adverse impacts related with the usage of anticancer medication were surveyed for half a year. The AEs most commonly experienced suggest that for all intents and purposes, all the patients accepting cytotoxic drugs suffered at least one AE. The critical announced MAE rates on our hospital ward (0.04% of medication administration and 0.03% MAE/patient admission) send out an impression of being generally low due to the

utilization of current security rules. Emphasize on deep understanding of MAE at individual foundations, is likely going to result in important procedure changes, improved effectiveness of MAE detailing, and various focal points.

Keywords: medication safety, chemotherapy drugs, adverse effects, side effects, error in prescription, error in administration, emetogenic chemotherapy, antiemetic drugs, and comparison of antiemetic guidelines

1. Introduction

Medication safety has been recognized to be important in the provision of patient care for a long time. With the evidence pointing to medication errors (MEs) as one of the leading causes of avoidable complications and deaths, there is a pressing need for a better understanding of the nature and scope of MEs, and the will to improve the current clinical delivery systems. [1]

The chemotherapeutic agents are associated with severe adverse effects (AEs), leading to economic burden and decreased quality of life. [2]

The issue of medication safety in chemotherapy drugs is highly significant when anticancer therapy is used as a treatment modality due to the high hazards derived from these agents and the disease context in which they are used. [2]

The purpose of this chapter is to determine the error rate in prescribing, dispensing and administration of chemotherapy drugs and related agents used in the treatment of cancer, and to promote the prevention of MEs to improve patient safety.

The complexity of treatment regimens designed to achieve the maximal anticancer effect balanced against acceptable toxicity leaves limited margin for error. Overdosing can result in death due to treatment associated AEs, while under dosing can have significant implications for the management of the disease and to the patient outcome. [3]

MEs can occur for a number of reasons. Errors can occur when human and system factors interact with the complex process of prescribing, dispensing and administration drugs, to produce an unintended and potentially harmful outcome.

With an extreme move in the comprehension of medical errors through the production of the 1999 Institute of Medicine (IOM) report, To Err is Human, [4], the IOM board required a change in the manner health-care experts comprehend therapeutic error by standards ranging from subjective psychology to human factors, and investigation of human execution in workplaces.

The enhancements in aeronautics and other security-arranged businesses, for instance, chemical engineering, manufacturing, and nuclear power, showed that complex systems, instead of individual specialists, were the fundamental wellsprings of error and thus an objective for improvement openings through modifications, systematization, and innovation. Sentinel events in oncology, including the death of Betsy Lehman in 1994 at Boston's Dana-Farber Cancer Institute, conspicuously highlighted the open impression of medicinal error. Past research has seemed certain patients are at an extended danger of preventable damage, which is associated with their restricted Physiological Reserve, (physiological reserve is the capacity of an organ or body part to fulfill its physiological activity), which typically joins patients with intense ailments, comorbidities, different prescriptions, and harmful sickness. [5, 6]

Chemotherapeutic prescriptions have a constrained therapeutic index and the dosage expected to give an effective response is conventionally poisonous to the body's quickly multiplying cells. The typical tissues antagonistically affected by

the chemotherapy drugs are those, which are rapidly partitioning, like bone marrow, gastrointestinal tract and hair follicles. Chemotherapy drugs also have other organ explicit toxicities. Moreover, a couple of drugs that are usually associated with speedy adverse reactions are a consequence of their biochemical nature, rather than their activity against tumors. The use of some cancer chemotherapy drugs have been associated with a few AEs, usually going from mild nausea to fatal myelosuppression. [7]

During the most recent decade, various examinations have shown that medication inducing morbidity and mortality is one of the most significant general medical issues. [8]

Clinicians should be aware that chemotherapy induced nausea and vomiting (CINV) is one of the most complicated side effects of chemotherapy. With the correct use of antiemetics, CINV can be prevented in almost 70% up to 80% of the patients. [9]

The goal of each antiemetic treatment is to abrogate nausea and vomiting. Twenty years back, nausea and vomiting were typical AEs resulting from specific sorts of chemotherapy and which obliged up to 20% of the patients to postpone or decay possibly corrective treatments [10]. Clinical and major research over the span of ongoing years has provoked persistent enhancements in the control of CINV. [11]

The improvement of the serotonin receptor antagonists (5-HT3RAs) in the mid-1990s was a standout among the most imperative advances in the chemotherapy of cancer patients. [12, 13] Another group of antiemetics discovered, the neurokinin1-receptor antagonist (NK1RA), and the essential medication in this class, aprepitant, were consolidated into the refreshed antiemetic rules. [14, 15]

In 1998, the main Multinational Association of Supportive Care in Cancer (MASCC) antiemetic rules reliant on the outcomes of the Perugia understanding, were brought together and were distributed worldwide, trailed by the American Society of Clinical Oncology (ASCO) rules in 1999 [16]. The two guidelines, similarly as the National Comprehensive Cancer Network (NCCN) rules, invigorated [17, 18]. The audit of antiemetics, contrasts these three rules, regarding the utilization of antiemetics in chemotherapy settings.

2. Medication error rate

The ME rate was dictated by ascertaining the level of errors. The numerators in the proportion, is the absolute number of error. The numerator in the proportion is the complete number of error that they watch, the denominator is called "opportunities for errors" and incorporates every single watched dosage that is controlled, in addition to the portions requested but not directed. [19, 20]

$$\text{Medication error rate} = \frac{\text{Number of errors observed}}{\text{Opportunities for errors}} * 100 \qquad (1)$$

Endorsing error happens at the time a prescriber orders a medication for a particular patient. The error might be due to dosage form, number of dosages, dose structure, course of association, and length of treatment. The MEs, including cancer chemotherapeutic administrators, may be particularly unsafe as these drugs have a limited helpful profile for which prescriptions have a confined association that may result in expanded toxicity and/or decreased tumor response. Furthermore, antineoplastic administrators are consistently coordinated to be

applied to more established patients with comorbidities and it is novel and complex treatment for nurses and medication assistants. Along these lines, antineoplastic masters are among the most outstanding reasons of ME. [1, 19, 20]

3. Theoretical framework

According to a study on MEs on a Community Hospital Oncology Ward, it was found that out of 141 medication administration errors (MAEs) detected amid the study period, the most persistent ones were administration errors, 41%, while 38% were either nurse or pharmacy dispensing errors, and 21% constituted order writing and transcribing errors. Out of these MAEs, only three errors resulted from adverse drug events. [20]

In another study based on the AEs.of.anticancer.drugs.in.an Oncology Centre of a Tertiary Care Hospital, from a total of 130 evaluated cases, 60 cases comprised males (46.2%), and 70 comprised females (53.8%). The most prevalent cancers among females were breast cancer and cervical cancer, whereas lung cancer and urinary bladder cancer were the most common among males. Nausea (48.5%), decreased appetite (39.2%), alopecia (37.7%), anemia (35.4%), vomiting (31.5%), and nail discoloration (30%) were the most frequently reported AEs. The commonly used pre medication were ondansetron, dexamethasone, aprepitant and proton pump inhibitors, individually or in combination. [21]

Moreover, a study regarding side effects of chemotherapy among cancer patients revealed that out of 99 patients, the majority had their age between 45–64 years (73.3%) and were females (93.3%). Nausea and vomiting were two of the most common side effects (83.3% and 78.9% respectively) reported.

Other common side effects were hair loss and loss of appetite. Also 6.7% of patients experienced peripheral neuropathy symptoms. [22]

3.1 Chemotherapy-induced emesis

With respect to the emetogenicity potential, the chemotherapy agents can be classified into four emetic risk groups: [23].

High (≥90% of patients experienced nausea and vomiting when no prophylactic antiemetic protection was provided);

Moderate (30–90% of patients experienced nausea and vomiting when no prophylactic antiemetic protection was provided);

Low (10–30% of patients experienced nausea and vomiting when no prophylactic antiemetic protection was provided);

Minimal (≤10% of patients, experienced nausea and vomiting when no prophylactic antiemetic protection was provided), as suggested by all three guidelines. [17, 18, 23, 24]. Hence, antiemetic prophylaxis is directly proportional to the emetogenic potential of the chemotherapy.

The emetogenic potential of the drugs is different in each guideline. In the MASCC guideline in particular, the emetogenic potential of oral chemotherapeutic agents is different from intravenous chemotherapeutic agents. In MASCC and NCCN guidelines, intravenous etoposide is labeled as having low emetogenic potential. However, oral etoposide is usually classified as having moderate emetogenic potential, implying that there is a 30%–90% incidence of emesis [24].

In a recently published study by Einhorn *et al*, [25] oral etoposide indeed seemed to have only low emetogenic potential. Additionally, althought imatinib is classified by the MASCC and NCCN guidelines as a moderate emetogenic agent, the daily use of antiemetics is not recommended in the special case of imatinib by the NCCN.

The ASCO guidelines do not implicate any of the oral chemotherapeutic agents in their classification system [23].

3.2 Patient-related risk factors inducing emesis

Patient-related risk factors, including age (young age usually experience more nausea and vomiting), gender (females generally experience more nausea and vomiting compared to males), a history of alcohol intake, a history of an emesis experience amid pregnancy, impaired quality of life, and also a history of previous chemotherapy, are known to increase the risk for CINV. [23, 26, 27]

3.3 Antiemetic agents

3.3.1 5-hydroxytryptamine receptor antagonists (5-HT3RAs)

These are the most effective antiemetic agents in the prophylaxis of acute CINV. [28]

The different 5-HT3RAs, namely dolasetron, granisetron, ondansetron, palonosetron and, tropisetron appear to be interchangeable. The lowest fully effective single dose for each agent should be use. The oral and intravenous routes are similarly effective. These statements are supported by all three guidelines. [29]

1. **Dolasetron:** All three guidelines recommend the same doses of dolasetron, which are 100 mg or 1.8 mg/kg intravenously, and 100 mg orally. [29]

2. **Granisetron:** All three guidelines recommend granisetron at a dose of 1 mg or 0.01 mg/kg intravenously, and 2 mg orally (MASCC and ASCO) or 1–2 mg orally (NCCN). [29, 30]

3. **Ondansetron:** with respect to the dosing of ondansetron, different statements are given. For example, the NCCN guidelines recommend ondansetron at a dose of 16–24 mg orally and 8–12 mg (maximum, 32 mg) intravenously, whereas the MASCC and ASCO guidelines recommend ondansetron at a dose of 24 mg orally (MASCC, 16 mg orally for moderately emetogenic chemotherapy) and 8 mg or 0.15 mg/kg I.V. In a recently published meta-analysis comparing low-dose ondansetron (8 mg) with high-dose ondansetron (24 or 32 mg), in a sub analysis in cisplatin based chemotherapy, high-dose ondansetron appeared to be more effective [29].

4. **Palonosetron:** All three guidelines recommend palonosetron at a dose of 0.25 mg intravenously. Oral palonosetron is not yet available. Palonosetron has a significantly longer half-life and a higher binding activity compared to the other 5-HT3RA. The actual role of palonosetron in comparison with the other available 5-HT3RA has been controversially discussed in the guidelines. However, none of the three guidelines designates a preferred 5-HT3RA, although palonosetron outperformed ondansetron and dolasetron in some secondary endpoints in one reported study. [29, 31]. For a better understanding, the results of the three available randomized studies with palonosetron in the acute phase are outlined, where it was found that palnosetron's effect was significantly superior to ondansetron. [29, 31, 32].

5. **Tropisetron:** An orally or intravenously dose of 5 mg is recommended for tropisetron according to the ASCO and MASCC guidelines. [29]

3.3.2 Steroids

Steroids are commonly used in the treatment of several cancers, such as lymphoma and leukemia as they help to destroy cancer cells and render chemotherapy more effective reduce allergy reaction to certain drugs, and also protect the patient from having nausea and vomiting after a round of chemotherapy. Steroids used in chemotherapy include prednisolone, methyl prednisolone, and dexamethasone. [33, 34]

Dexamethasone: Although not approved as an antiemetic, dexamethasone plays a major role in the prevention of acute and delayed CINV and is an integral component of almost all antiemetic regimens [33, 34]. All three guidelines recommend the use of dexamethasone for the acute prevention of highly, moderately, and low emetogenic chemotherapy.

According to the three guidelines, for the prevention of delayed emesis, dexamethasone is recommended in combination with aprepitant for highly emetogenic chemotherapy (MASCC, ASCO, NCCN), but not for moderately emetogenic chemotherapy (MASCC, ASCO). Only the NCCN guidelines suggest dexamethasone as a possible combination partner for aprepitant with moderately emetogenic chemotherapy.

This recommendation of the MASCC and ASCO expert panel is mostly drive by the study of Warr *et al*. [35] in patients receiving moderately emetogenic chemotherapy. In this study, aprepitant is given as monotherapy for the prevention of delayed CINV, and a complete response rate of 55%, in comparison with 49% for ondansetron, was achieved in the delayed phase.

This result might suggest that the combination of dexamethasone and aprepitant in the delayed phase would have greater antiemetic efficacy. Thus this might be the reason why the NCCN panel was recommending this combination in the moderately emetogenic setting in the delayed phase.

Further studies are warranted to clarify this clinically important question. When combined with aprepitant, dose reduction of dexamethasone (dexamethasone is a sensitive substrate of the cytochrome P450 [CYP450] 3A4 enzyme) has to be undertaken. For the prevention of acute CINV, the dose of choice should be 20 mg of dexamethasone (12 mg when co administered with aprepitant). For highly emetogenic chemotherapy a single dose of 8 mg dexamethasone (12 mg in the NCCN guidelines) is enough. For moderately emetogenic chemotherapy, these dose recommendations were largely driven by studies from the Italian Group for Antiemetic Research [36, 37].

3.3.3 Neurokinin 1 receptor antagonists (NK1RAs)

NK1 receptor antagonists are in a class of drugs used to treat nausea and vomiting associated with chemotherapy. Aprepitant, casopitant, fosaprepitant, and rolapitant are some examples of NK1 drugs.

Aprepitant: Is the first representative of this new group that blocks the NK1 receptor in the brainstem emetic center and gastrointestinal tract [38]. So far, it is only available for oral use and should be administered as 125 mg on day one, and 80 mg on day two and day three as recommended by all three guidelines. Published studies have shown that the addition of NK1RAs to standard antiemetic therapy (5HT3RA plus dexamethasone) appears to have a significant effect in controlling cisplatin-induced acute as well as delayed emesis.

In all studies the aprepitant regimen was more pronounced in the delayed phase of CINV [38–40]. The use of aprepitant is suggested for both highly and moderately emetogenic chemotherapy by all three guidelines.

In the moderately emetogenic setting, one study has been published and, formed the basis for the recommendation of aprepitant for anthracycline and

cyclophosphamide– based emetogenic chemotherapy. In this study [35], the triple combination of ondansetron, dexamethasone, and aprepitant used in the first 24 hours, followed by aprepitant monotherapy for another 2 days, proved to be superior to the whole 5-day study period (51% *vs* 42%). However, no significant differences were observed in the delayed period (49% *vs* 55%), possibly because only patients receiving an anthracycline and cyclophosphamide– based regimen were included in this study.

The MASCC and ASCO guidelines restricted the recommendation of the triple combination in the moderately emetogenic setting due to this "high-risk" chemotherapeutic regimen.

The NCCN guidelines, however, recommended aprepitant in the moderately emetogenic setting in selected patients based on the emetogenic potential of the chemotherapy.

In the MASCC guidelines, it was noted that no trials have compared so far, the combination of aprepitant with dexamethasone for delayed emesis with the previous standard of dexamethasone combined with a 5-HT3RA in highly emetogenic chemotherapy. [16] In the meantime, a study addressing this question [40] showed that the effect obtained from the combination of aprepitant with dexamethasone was superior to one resulting from the combination of ondansetron and dexamethasone in the delayed phase.

Aprepitant is a moderate inhibitor of CYP3A4; therefore, the dexamethasone dose has to be reduced, as discussed before. Theoretical concerns that aprepitant might interact with chemotherapeutic agents could not be demonstrated in preclinical and clinical studies so far [16, 40, 41].

3.3.4 Metoclopramide

Metoclopramide was part of the former MASCC, ASCO, and NCCN guidelines and was suggested for the prevention of delayed emesis [16, 20]. Although metoclopramide has proved to be as effective as 5-HT3RA when combined with steroids in the prevention of delayed CINV [42, 43] it is not recommended in the new guidelines in this setting. However, because 5-HT3RAs are recommended as an alternative to dexamethasone in the delayed phase for moderately emetogenic chemotherapy, metoclopramide might also be an adequate alternative, although not recommended by the guidelines.

3.3.5 Cannabinoids

The MASCC guidelines state that cannabinoids can be considered for refractory nausea and vomiting and as a rescue antiemetic. However, due to the weak antiemetic efficacy with potentially high side effects including, sedation, euphoria, dysphoria, dizziness, and hallucination, cannabinoids are not recommended as first-line treatment for the prevention of CINV.

In the ASCO and NCCN guidelines, cannabinoids are advised in patients intolerant or refractory to 5-HT3RAs or steroids and aprepitant.

Interestingly, a systematic review addressing the efficacy of oral cannabinoids in the prevention of nausea and vomiting revealed, that cannabinoids were slightly more efficient than conventional anti emetics (e.g., metoclopramide, phenothiazines, haloperidol.). However, their usefulness was generally limited by the high incidence of toxic effects, such as dizziness, dysphoria, and hallucinations. [44–46]

3.3.6 Benzodiazepines

Benzodiazepines can be useful in controlling anxiety and reduction of anticipatory CINV or in patients with refractory and breakthrough emesis, as suggested by all three guidelines. [47]

3.3.7 Antihistamines

The most common antihistamines used are diphenhydramine and hydroxyzine. Nevertheless, the available studies have not shown any significant antiemetic activity in these agents. [48]

3.3.8 Olanzapine

Olanzapine is an atypical antipsychotic drug with, antiemetic potential due to its action at multiple receptor sites implicated in the control of nausea and vomiting. [49] In a phase II trial where olanzapine was used in combination with granisetron and dexamethasone for the prevention of CINV, the combination therapy proved to be highly effective in controlling acute and delayed CINV in patients receiving highly and moderately emetogenic chemotherapy. [50] The latest phase II study published by Navari *et al*. [51] showed exceptionally high complete protection rates from both acute and delayed CINV when using a combination of palonosetron (day 1), dexamethasone (day 1), and olanzapine (days 1–4) in patients receiving highly or moderately emetogenic chemotherapy. Consequently, olanzapine is mentioned by the MASCC and NCCN guidelines for the treatment of refractory and breakthrough emesis with a suggested dose of 2.5–5 mg.

3.4 Classification of CINV based on the guidelines

According to the guidelines CINV can be differentiated into five categories: [52].

1. When nausea and vomiting occur within 24 hours of initial administration of chemotherapy is known as acute onset, which is mostly due to serotonin-related agents.

2. When nausea and vomiting occur 24 hours to several days after initial treatment is known as delayed onset, which is due to substance P-related agents.

3. Anticipatory nausea and vomiting is observed in patients whose emetic episodes were triggered by taste, odor sight, thoughts, anxiety, or had a history of poor response to antiemetic agents or received inadequate antiemetic prophylaxis in the previous cycle of chemotherapy.

4. Breakthrough CINV is defined as vomiting and/or nausea that occur within five days of chemotherapy administration after the use of guideline directed prophylactic antiemetic agents. This type of CINV usually requires immediate treatment or requires "rescue" with additional antiemetics.

5. Refractory CINV is defined as vomiting and/or nausea occurring after chemotherapy, usually in subsequent chemotherapy cycles after guideline directed prophylactic antiemetic agents have failed in earlier cycles.

3.5 Prevention of CINV

3.5.1 Regimens linked to a high incidence of nausea and vomiting are referred as highly emetogenic chemotherapy (≥90%)

Acute CINV: All three guidelines suggest the combination of a 5-HT3RA, dexamethasone, and aprepitant within the first 24 hours of chemotherapy.

Delayed CINV: All three guidelines suggest the combination of dexamethasone and aprepitant for delayed CINV. Trials have indicated that from 60% to nearly 90% of patients receiving cisplatin will experience delayed emesis if not given preventive anti emetics. Therefore, appropriate prophylaxis is necessary [17, 52, 53].

3.5.2 Regimens linked to a moderate incidence of nausea and vomiting are referred as moderately emetogenic chemotherapy (30–90%)

Acute CINV: All three guidelines recommend the combination of a 5-HT3RA plus dexamethasone with or without aprepitant for acute CINV. However, the key question in this setting is whether aprepitant should be part of the antiemetic prophylaxis or not. The ASCO and MASCC guidelines recommend the triple combination (a 5HT3RA, dexamethasone, and aprepitant) for patients receiving the combination of an anthracycline and cyclophosphamide–based regimen. The NCCN guidelines, however, broadened the spectrum of the use and suggest using the triple combination in patients receiving other chemotherapy agents of moderately emetogenic risk like carboplatin, epirubicin, ifosfamide, or irinotecan [17, 52, 53].

Delayed CINV: Dexamethasone is the preferred agent to be used for delayed CINV. Nonetheless, when aprepitant is used for the prevention of acute CINV then it should also be used for the prophylaxis of delayed CINV as mono therapy, as stated by the MASCC and ASCO guidelines. As discussed before, the NCCN guidelines suggest aprepitant with or without dexamethasone in this situation. A 5-HT3RA can be used as an alternative, although their therapeutic role in the delayed phase is rather limited [34]. In contrast to all three previously published guidelines, metoclopramide is not reflected in the new guidelines as an alternative option [17, 52, 53].

3.5.3 Regimens linked to a low incidence of nausea and vomiting are referred as low emetogenic chemotherapy (10–30%)

The MASCC and ASCO guidelines in unison recommend the use of a steroid alone in the first 24 hours and no prophylaxis beyond 24 hours for acute CINV. The NCCN guidelines recommend prochlorperazine or metoclopramide as well, as alternative drugs to dexamethasone [17, 52, 53].

3.5.4 Regimens linked to a minimal incidence of nausea and vomiting are referred to as minimally emetogenic chemotherapy (≤10%)

All three guidelines suggest that, for patients treated with agents of low emetic risk, no antiemetic drugs should be routinely administered before chemotherapy [17, 52, 53].

3.5.5 Regimens linked to an incidence of nausea and vomiting in case of anticipatory, breakthrough or refractory chemotherapy

Anticipatory, breakthrough and refractory CINV:

Anticipatory CINV is mostly seen in patients with anxiety or patients who did not receive adequate antiemetic prophylaxis in the previous cycle [17, 52, 53].

Breakthrough CINV is defined as an event that happens in spite of optimal preventive treatment.

Refractory CINV is nausea and vomiting that recurs in subsequent cycles of therapy when all previous preventive and rescue treatments fail.

If optimal treatment has been given as prophylaxis, repeated dosing of the same agents is unlikely to be successful; the addition of dopamine-receptor antagonists

(for instance, metoclopramide) might be useful, or the addition of other agents such as benzodiazepines or neuroleptics. Olanzapine, an atypical neuroleptic, could also be considered, as suggested by the MASCC and NCCN guidelines. [16]

3.5.6 Regimens, linked to CINV in case of receiving chemotherapy more than one day in a cycle

Multiple-Day chemotherapy: for patients receiving multiple day chemotherapy like, for instance with cisplatin, the MASCC guidelines recommend the use of a 5-HT3RA in combination with dexamethasone for acute CINV and dexamethasone alone for delayed CINV. The use of NK1RAs remains to be defined, as stated by the MASCC guidelines. However, the NCCN guidelines advise the application of aprepitant for at least the first 3 days, in analogy to highly emetogenic chemotherapy. Furthermore, the NCCN guidelines clearly mention the use of palonosetron in this setting [17, 52, 53].

4. MEs involving antineoplastic agents

MEs involving cancer chemotherapy agents may be particularly harmful as these drugs have a narrow therapeutic index for which incorrect dosing or administration may result in increased toxicity and/or decreased tumor response. In addition, antineoplastic agents are often administered to older patients with comorbidities and may be part of novel and complex treatment protocols less familiar to nurses and pharmacists. As a result, antineoplastic agents are among the most common causes of ME-related deaths. These concerns have led to an update of national guidelines, including recommendations for a systems approach consisting of multidisciplinary monitoring of medication use, prescribing guidelines, preparation and dispensing methods, and medication administration. [54]

5. Materials and methods

An imminent, observational, non-interventional study was led at the Oncology Department, Baptist Hospital, Bangalore for half a year. All patient related- data was gathered according to case record structure. During a 6 months period, I directed an imminent report on the Oncology Ward in a Tertiary Care Hospital, with the following objectives:

- Complete reporting of prescription errors
- Classify prescription errors
- Complete revealing of MAEs errors detected by nurses
- Classify watched MAEs, and
- Formulate improvement procedures.
- Monitor and register the occurrence of side effects
- Assess how to overcome side effects?
- Evaluate the antiemetic treatments used,

A survey review of a self-assertively picked test of 70 chemotherapy solicitations to assess the appropriateness of mentioning and administering was conducted. An aggregate of 70 patients getting chemotherapy met for information on sort of side effects, MEs and other pertinent relevant information like, diagnosis, treatment, drugs utilized, and arrangement with the AEs were assembled from the patient's medical records. The data was arranged reliant on various parameters.

The MAEs are described as a preventable oversight in medicine association due to error beginning in requesting, apportioning, or overseeing. It includes association of (1) wrong prescription, (2) wrong dose, (3) wrong route, (4) wrong time, (5) a medication to which the patient has a known sensitivity, as well as, (6) a prescription with multiple drugs cooperation with another prescription. The patients accepting investigation included patients with affirmed malignancies who confessed that go chemotherapy in oncology wards.

As we expect to survey the resulting side effects a 6 month examination period was arranged. The number of patients getting chemotherapy in oncology ward for a half-year time span were utilized to appraise the sample measure.

6. Results and discussion

6.1 Demographic details

Age and sex:

Among the 70 patients, 22(31.4%) were males and 48(68.57%) were females. A further order dependent on the age uncovered that in the majority of the patients, both males and females were in the age range of 20–65 years. (**Table 1**).

Number of chemotherapy cycles:

Among the 70 patients, 14(20%) had only one chemotherapy cycle. 16(22.85%) had two chemotherapy cycles, 16(22.85%) had three chemotherapy cycles, 5(7.14%) had four chemotherapy cycles, 6(8.57%) had five chemotherapy cycles, 9(12.85%) had six chemotherapy cycles and, 4(5.71%) had more than six cycles of chemotherapy, mostly due to maintenance chemotherapy.

6.2 Chemotherapy agents

The most common endorsed chemotherapy agents in our setting.were.cisplatin (21.42%), carboplatin (17.14%), paclitaxel (14.28%), oxaliplatin.(12.85%), doxorubicin.(11.42%), and docetaxel.(11.42%), as it can be observed in **Table 2** and **Figure 1**.

6.3 Clinical diagnosis of the patients

The sub-classification based on the gender, revealed that breast (24.28%), blood and bone marrow (5.71%), cervical (2.85%), ovarian (2.85%), lung (2.85), non-Hodgkin lymphoma (2.85%), colon (2.85%), stomach (2.85%), and esophageal (2.85%) cancers

Age group (years)	Number of patients	% of patients
Pediatric (0–20)	5	7.14
20–65	58	82.85
Geriatric (< 65)	7	10

Table 1.
Cancer patient's distribution according to the age groups.

Name of drug	No of prescription	% of prescription
Cisplatin	15	21.42
Carboplatin	12	17.14
Paclitaxel	10	14.28
Oxaliplatin	9	12.85
Docetaxel	8	11.42
Doxorubicin	8	11.42
Cyclophosphamide	7	10
Vincristine	5	7.14
Etoposide	4	5.71
Flurouracil	3	4.28
Ifosfamide	3	4.28
Leucovorin	3	4.28
Methotrexate	3	4.28
Zoledronic acid	3	4.28
Atgam	2	2.85
Bendamustine	2	2.85
Daunorubicin	2	2.85
Epirubicin	2	2.85
Pemetrexed	2	2.85
Vinorelbine	2	2.85
Rituximab	2	2.85
Anastrozole	1	1.42
Bleomycin	1	1.42
Bortezomib	1	1.42
Gemcitabine	1	1.42
Herceptin	1	1.42
Irinotican	1	1.42

Table 2.
Chemotherapy agents used in the setting.

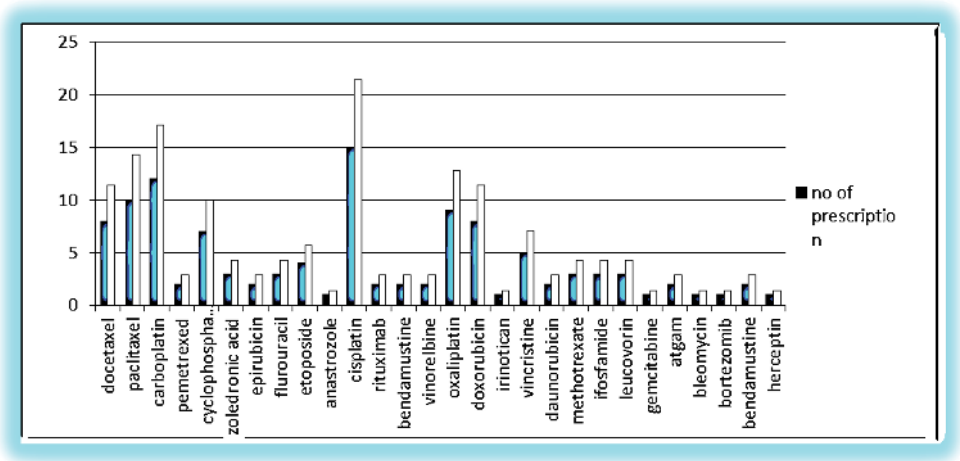

Figure 1.
Prevalence of the chemotherapy agents used in the setting according to number of prescriptions.

Type of cancer	Number of females	Number of males	% of female patients	% of male patients
anorectal	0	1	0	1.42
brain	1	0	1.42	0
breast	17	0	24.28	0
blood and bone marrow	4	3	5.71	4.28
bone	0	1	0	1.42
cervical	2	0	2.85	0
colon	2	2	2.85	2.85
esophageal	2	0	2.85	0
head and neck	1	1	1.42	1.42
Hodgkin lymphoma	1	1	1.42	1.42
larynx	0	1	0	1.42
lung	2	2	2.85	2.85
lupus	1	0	1.42	0
neck	1	0	1.42	0
non Hodgkin lymphoma	2	2	2.85	2.85
oral	1	2	1.42	2.85
ovarian	2	0	2.85	0
peritoneal	1	0	1.42	0
testicular	0	1	0	1.42
thyroid	0	1	0	1.42
tongue	0	1	0	1.42
tonsil	1	1	1.42	1.42
uterus	1	0	1.42	0
rectal	0	1	0	1.42
skin	0	1	0	1.42
muscle	1	0	1.42	0
soft tissue	1	1	1.42	1.42
stomach	2	0	2.85	0

Table 3.
Cancer prevalence among the study patients.

were the most prevalent types of cancer in females. On the other hand, blood and bone marrow (4.28%), lung (2.85%), non-Hodgkin lymphoma (2.85%), colon (2.85%), and oral (2.85%) cancers were the most prevalent in males as it can be seen in **Table 3**.

Furthermore, the most common type of cancer in the age group of 0–20 years was blood and bone marrow cancer (4.28%), while within the age group 20–65 years was breast cancer (24.28%) in females and oral cancer (2.85%) in males. In addition, in adults over 65 years breast cancer (2.85%) was the most prevalent in females. While in men there was not any significant type, as the occurrence of all the cancer types were shown to be equal (**Figure 2**).

6.4 Side effects

According to **Table 4**, the most influenced organ framework in both females and males was gastro intestinal tract (GIT), trailed by skin and subcutaneous tissue, musculoskeletal, blood, and nervous systems. Most of the patients have suffered the side

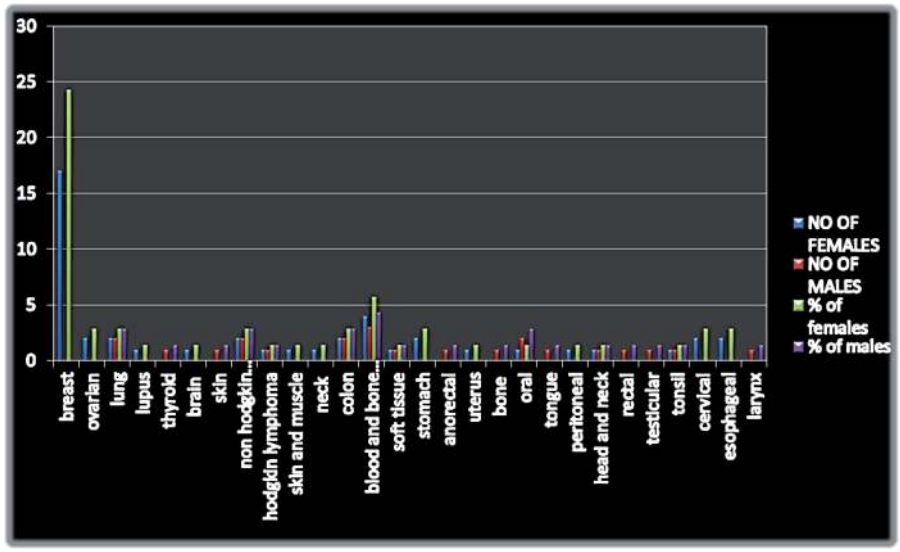

Figure 2.
Cancer prevalence among the study patients according to gender.

Organ system	side effect	Number of patients	% of patients
ALLERGIC REACTIONS	Anaphylaxis	4	5.71
	Hot flashes	1	1.42
	Itching	2	2.85
	Rash	3	4.28
	Redness	4	5.71
	Serum sickness like syndrome	2	2.85
	Swelling	5	7.14
ASTHENIA (weakness) AND CHRONIC PAIN	Fatigue	2	2.85
	Feeling weak or tired	19	27.14
	Fibromyalgia (pain all over the body)	43	61.42
BLOOD AND LYMPHATIC DISORDERS	Anemia	14	20
	Bleeding	20	28.57
	Bone marrow depression (myeloid suppression)	3	4.28
	Hemolysis	2	2.85
	Leukopenia	5	7.14
	Risk of infection	16	22.85
	Thrombocytopenia (low platelet count)	4	5.71

Organ system	side effect	Number of patients	% of patients
GIT DISORDERS	Abdominal pain	17	24.28
	Constipation	17	24.28
	Decreased appetite	32	45.71
	Diarrhea	52	74.28
	Nausea	62	88.57
	Vomiting	65	92.85
HEART AND BLOOD VESSELS DISORDERS	Chest pain	1	1.42
	Low blood pressure	16	22.85
HORMONAL DIORDERS	Missed menstrual period	3	4.28
INFECTIONS	Anal ulceration	1	1.42
	Chills	6	8.57
	Fever	7	10
	Sore eye	1	1.42
	Sore mouth	15	21.42
	Chronic wound (a wound that will not heal)	3	4.28
LIVER DISORDERS	Hepatic dysfunction	2	2.85
METABOLISM AND NUTRITIONAL DISORDERS	Anorexia	2	2.85
	Loss of taste	12	17.14
MUSCULO SKELETAL & CONNECTIVE TISSUE DISORDERS	Joint pain	17	24.28
	Muscle pain	9	12.85
NERVOUS SYSTEM DISORDERS	Dizziness	2	2.85
	Headache	2	2.85
	Insomnia	2	2.85
	Neuropathy	15	21.42
PULMONARY DISORDERS	Respiratory distress	4	5.71
RENAL &URINARY DISORDERS	Bladder irritation	2	2.85
	Blood in urine	7	10
SKIN & SUBCUTANEOUS TISSUE DISORDERS	Alopecia (hair loss)	25	35.71
	Bruising	18	25.71
	Change in skin color	3	4.28
	Nail discoloration	15	21.42
	Sweating	1	1.42

Table 4.
Side-effects prevalence and distribution depending on the organ system.

effects related to GIT, such as nausea, vomiting, diarrhea and decreased appetite. The majority of the patients experienced pain all over the body, especially in the muscle and joints and most of the patients experienced alopecia (temporary hair loss).

There are many side effects resulting from the use of chemotherapeutic agents, and rapidly developing cells have been shown to be highly affected by these agents. Hair follicles, skin, and the cells that line the GIT are some examples of the fastest growing cells in the human body, and therefore are more sensitive to the effects of chemotherapy. For this reason patients may experience hair loss, rashes, and diarrhea, respectively.

6.5 Antiemetics

6.5.1 Antiemetic therapy

Our analysis showed that all of the patients have used anti emetics in their treatment. The antiemetic used, was either a single anti emetic or a combination of antiemetics. Ondansetron was prescribed for 81.42% of the patients and used at doses of 8 mg and 16 mg, of which 8 mg was most commonly prescribed in patients recommended with a single antiemetic treatment, while the utilization of 16 mg was applied in medications containing more than one antiemetic. Dexamethasone was endorsed in 44.28% of the patients with a range of 4mg - 20 mg. Among these, 8 mg was the most normally utilized dose separately, as well as in combination with other agents. The other antiemetic, aprepitant represented 24.28% of the medications. Palonosetron was also recommended in this setting.

Aside from the antiemetics, other premedication utilized were Pantoprazole 20 mg and 40 mg, Ranitidine 150 mg and Rabeprazole 20 mg. Of these Pantoprazole, 40 mg was the most commonly used, representing 72.85% of the total prescriptions.

6.5.2 Emetogenicity and antiemetics

The utilization of more up to date antiemetic agents has profoundly diminished the occurrence of nausea and vomiting in patients receiving chemotherapy, although these symptoms were not completely forestalled. All of the patients got an antiemetic medication preceding the chemotherapy.

A 5-HT3RA like Ondansetron, Palonosetron, and a steroid drug such as dexamethasone and Aprepitant were the normally endorsed premedication in our setting, either separately or in combination. The main high hazard associated emetogenic tranquilizer used in chemotherapy in our investigation was Cisplatin. The premedication generally recommended for this setting was Ondansetron 16 mg and Dexamethasone 8 mg either separately or in combination. Cyclophosphamide, Carboplatin, Doxorubicin, Epirubicin, Oxaliplatin, Cytarabine and Ifosfamide were the drugs used in cases of moderate emetogenicity. In this study, the premedication used by the patients were Ondansetron with 8 mg and 16 mg doses, Dexamethasone with 4 mg, 8 mg, 16 mg, and 20 mg doses, Palonosetron with 0.25 mg dose and Aprepitant with 125 mg dose.

6.6 Medication errors

In this project, the error percentage in the prescription as well as in the administration of chemotherapy drugs in an oncology ward was also established.

6.6.1 Prescription error

The total error percentage reported in relation to the total number of prescriptions (70) was of 24.28%.

From these total error percentage 10% were due to drug–drug interaction, 2.8% to an unclear read, 2.8% of to lack of patient's age,2.8% to poorly written medication order, 1.42% to lack of date, and 1.4% to a bad hand writing, making it difficult to read. A complete list of errors and their associated percentage is presented in **Table 5**.

6.6.2 Administration error

Drug administration is performed by nurses. The total error percentage reported in administration of chemotherapy drugs in all the 70 patients under study was of 11.42%, out of which 2.85% were due to wrong administration dose, 2.85% to drug administration outside the guidelines, 1.42% to errors related to the speed in drug administration, and 1.45% to wrong administration technique. A complete error list is displayed in **Table 6**.

6.6.3 Prevention of medication errors

Currently, there are no sufficient strategies for estimating ME rates, and an assortment of self- reporting and non- self-reporting approaches should be utilized. The repeat of declared MEs, made the health care system to check carefully the

Type of error	Number of errors	% of errors
Wrong drugs written on prescription	0	0
Dose of drug	0	0
Dosage of drug(inappropriate or wrong dosage forms written on prescription)	0	0
Route of drug	0	0
Frequency	0	0
Date	1	1.42
Lack of patient's gender	0	0
Lack of patient's age	2	2.85
Ilegible (not clear enough to read)	2	2.85
Error in allergy documented	0	0
Error in location of treatment order	0	0
Nonstandard abbreviation used	0	0
Presence of therapeutic duplication, if any	0	0
Drug interaction if any	7	10
Food drug interaction if any	0	0
Signature of drug	0	0
Poorly written medication order	2	2.85
Miss interpreted handwritten ME	1	1.42
Fails to complete order	2	2.85
Total counts	17	24.28

Table 5.
Types of medication error possible to occur in drug prescription.

Type of error	No. of errors	% of errors
Wrong drugs administration by nurses	0	0
Wrong dosage administration for a recommended drugs by nurses	0	0
Failure to give a drug by the health care supplier	1	1.42
Wrong dose administration	2	2.85
Wrong administration technique	1	1.42
Drug administration to the wrong patient	0	0
Medication discontinuation failure	0	0
Omission (failure to administer an ordered dose before the next scheduled dose)	1	1.42
Double dosing by nurses	0	0
Use of incorrect (wrong)drug vehicle	0	0
Drug administration after a discontinuation order	0	0
Administration of incompatible medication	0	0
Drug administration without a physician order	0	0
Drug administration outside the established guidelines	2	2.85
Administration of an expired drug	0	0
Error in the speed of drug administration	1	1.42
Food-drug interaction	0	0
Total Counts	8	11.42

Table 6.
Types of medication errors possible to occur in drug administration.

quality with which MEs are looked for, the procedure used, the patient populace, and the importance of errors.

We have concluded that a nurse is the perfect single individual to detect a ME. Firstly, by routinely surveying the suitability of the medication and differentiating the substituted drug to the doctor-composed request. Although, the nurse may be accused of assessing the whole procedure between request composing and apportioning and afterwards, the association system.

Secondly, nurse ME declaration is the transcendent strategy in many, if not most restorative centers, give it ponder for understanding and improving the medical caretaker, revealing procedure of progressively summed up application.

Thirdly, although disliking, everyone should clearly promote a ME presentation/reduction. The ME aversion is an essential activity and a fundamental piece of significant worth in nursing. As O'Shea has noted, a nurse is accountable and responsible for the drug administration and ME anticipation is currently considered as a national nursing basic. [20]

Taking into account the jobs of drug specialists and nurses in MAE revealing cover, the benefit of including the drug store, at any foundation, would be conversely related to the adequacy of nurse reporting. Considering our decreased

rate of reporting late organizations, our MAE rates are presumably similar to those detailed from different programs with compelling interception systems in place. In total, the prescribed current benchmarks displayed error rates of about 5% for association plus intercepted MEs, and roughly 0.1% to 0.2% for MAEs. These numbers appear to be commonly autonomous of patient age and chemotherapy *versus* non-chemotherapy solutions. For organization plus captured MEs, type 1 errors have been commonly typical. [a type I error is when a researcher rejects the null hypothesis that is actually true in reality. In other words, a type I error is a false positive or the conclusion that a treatment does have an effect, when in reality it does not have].

Our investigation shows that the MAE may fundamentally move toward nurse dispensing and organization. Our outcomes propose that in order to improve the formulation of MAE prevention strategies, each therapeutic center should initially be aware of where in the process of mentioning, apportioning, and overseeing medicines, the overwhelming number of MAEs starts.

6.7 Adverse effects

The overall AEs observed in both genders were practically identical. Nevertheless, the effects on gastro intestinal tract and musculoskeletal system were higher in females, which may be explained by a higher affectability of this gender by these particular effects. Iron deficiency is seen as a moderately basic condition in patients with disease, particularly those with solid tumors, lymphomas and receiving myeloid suppressive chemotherapy. Treatment for chemotherapy-induced anemia (CIA) started when the hemoglobin level fell beneath 12 mg/dl with oral or intravenous iron enhancements. Blood transfusions were picked in serious cases. In our setting, the specialists generally recommended ferrous sulfate, folic acid and Vitamin B12 prophylactic estimates, for example, great oral hygiene, avoidance of spicy food, and utilization of mild-flavored toothpaste and saline peroxide mouthwashes 3 or 4 times per day, ingrained where appropriate for limiting oral mucositis.

7. Conclusions

The AEs related with the utilization of anticancer drugs were assessed during half a year. The AE prevalence encountered and experienced suggests that all patients getting cytotoxic medication may endure at any rate one AE. Nausea, vomiting, decline appetite, alopecia, anemia, nail discoloration and anorexia were the most prevalent AEs detected. Correlation of the AEs observed with the group of individuals to achieve larger purpose did not show some new AEs. The frequency of AEs has shown to be extensively high and arouse from the utilization of existing premedication. Given the disclosures of the examination, the attempts to confine the AEs related with the anticancer medicines ought to be centered around. Expanding the mindfulness through informative intercession, actualize proper usage of premedication and non- pharmacological treatment are essential for improved personal satisfaction. Treatment rules are noteworthy in light of the fact that they outfit clinicians with a movement of proposition made from the international expert's dependent on their elucidation of the latest clinical trial data. In spite of certain qualifications among the MASCC, ASCO, and NCCN rules, all gave invigorated references and proposals to direct the perfect use of

antiemetics. Nevertheless, the necessity for a progressively and reasonable usage of treatment rules is critical to improve the nature of thoughts of cancer patients. Significant detailed MAE rates on our hospital ward (0.04% of medication organizations and 0.03 MAEs/patient admission.) have all the earmarks of being generally low due to the use of current security rules. An accentuation on contemplating MAEs at individual foundations is probably going to result in significant technique changes, improved effectiveness of MAE revealing, and various other advantages.

8. Limitation

The major limitation of the study was the inability to distinguish between immediate and delayed AEs due to the difficulty of the patients in recall the AE's.

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In Memory of My Grandfather Fathollah Namjoo Kerman

But grandpa's *not truly gone. Because his memory lives on. In all of us who loved him.*

Acronyms and Abbreviations

AE	Adverse effect
ASCO	American society of clinical oncology
CIA	Chemotherapy induced anemia
CINV	Chemotherapy induced nausea and vomiting
GIT	Gastro intestinal tract
IOM	Institute of medicine
MAE	Medication administration error
ME	Medication error
MASCC	Multinational association of supportive care in cancer
NCCN	National comprehensive cancer network
NK1RAs	Neurokinin 1-receptor antagonists
5-HT3RAs	Serotonin receptor antagonists

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References

[1] Medication Safety in Hospitals: Avoiding Medication Errors in the Medication use Process 201310.4172/2167-1052.1000134Advances in Pharmacoepidemiology and Drug Safety

[2] Prevalence and significance of potential drug-drug interactions among cancer patients receiving chemotherapy 2020Mohammad Ismail, Sehrash Khan, Fahadullah Khan, Sidra Noor, Hira Sajid, Shazia Yar, Irum Rasheed10.1186/s12885-020-06855-9BMC Cancer

[3] Potential drug–drug interactions in hospitalized patients undergoing systemic chemotherapy: a prospective cohort study, 2015, Paula Stoll, Luciane Kopittke, 10.1007/s11096-015-0083-6 International Journal of Clinical Pharmacy

[4] To Err Is Human: building a safer health system Kohn L T Corrigan J M Donaldson M S Washington DC USA: Institute of Medicine/National Academy Press ISBN 0 309 06837 1

[5] Incidence of Adverse Events and Negligence in Hospitalized Patients 1991Troyen A. Brennan, Lucian L. Leape, Nan M. Laird, Liesi Hebert, A. Russell Localio, Ann G. Lawthers, Joseph P. Newhouse, Paul C. Weiler, Howard H. Hiatt10.1056/nejm199102073240604New England Journal of Medicine

[6] Quality in Australian Health Care Study 1996Ross McL Wilson, William B Runciman, Robert W Gibberd, Bernadette T Harrison, John D Hamil ton10.5694/j.1326-5377.1996.tb122287.xMedical Journal of Australia

[7] Neurological adverse effects of cancer chemotherapy, 2013, Adam C.G. Thomas, 10.1097/fad.0b013e32835ed7b5 Adverse Drug Reaction Bulletin

[8] Preventing drug-related morbidity - the development of quality indicators, 2003, C. J. Morris, J. A. Cantrill, 10.1046/j.1365-2710.2003.00496.x, Journal of Clinical Pharmacy and Therapeutics

[9] Chemotherapy-Induced Nausea and Vomiting: Time for More Emphasis on Nausea? , 2015, Terry L. Ng, Brian Hutton, Mark Clemons, 10.1634/theoncologist.2014-0438, The Oncologist

[10] Global cancer statistics 2011 Ahmedin Jemal, Freddie Bray, Melissa M. Center, Jacques Ferlay, Elizabeth Ward, David Forman 10.3322/caac.20107 CA: A Cancer Journal for Clinicians.

[11] Emetogenicity of multiday chemotherapy regimens: Drug and patient factors affecting control of CINV 2009J. D. Howell, H. Brown10.1200/jco.2009.27.15_suppl.e20683Journal of Clinical Oncology

[12] Serotonin Receptor Subtypes Involved in the Elevation of Serum Corticosterone Concentration in Rats by Direct- and Indirect-Acting Serotonin Agonists, 1990, Ray W. Fuller, Harold D. Snoddy 10.1159/000125586, Neuroendocrinology

[13] How serotonin receptors regulate morphogenic signalling in neurons, 2017, Alexander Wirth, Katrin Holst, Evgeni Ponimaskin, 10.1016/j.pneurobio.2016.03.007, Progress in Neurobiology

[14] Aprepitant: novel anti-emetic brings, greater benefit for chemotherapy recipients, 2003, RM Poole, 10.2165/00128413-200314000-00029, Inpharma Weekly

[15] Aprepitant reduces nausea and vomiting after chemotherapy, 2003,

&NA, 10.2165/00128413-200313960-00032 Inpharma Weekly

[16] Prevention of chemotherapy- and radiotherapy- induced emesis: results of the 2004 Perugia International Anti-emetic Consensus Conference 200610.1093/annonc/mdj078Annals of Oncology

[17] ASCO, NCCN, MASCC/ESMO: a comparison of anti-emetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients, 2018 Yasmeen Razvi, Stephanie Chan, Thomas McFarlane, Erin McKenzie, Pearl Zaki, Carlo DeAngelis, William Pidduck, Ahmad Bushehri, Edward Chow, Katarzyna Joanna Jerzak, 10.1007/s00520-018-4464-y, Supportive Care in Cancer

[18] Bridging the Critical Divide in Pain Management Guidelines From the CDC, NCCN, and ASCO for Cancer Survivors, 2018, Salimah H. Meghani, Neha Vapiwala, 10.1001/jamaoncol.2018.1574, JAMA Oncology

[19] Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality 1997D. C. Classen10.1001/jama.277.4.301JAMA: The Journal of the American Medical Association

[20] Study of Medication Errors on a Community Hospital Oncology Ward 2006 Clyde D. Ford, Julie Killebrew, Penelope Fugitt, Janet Jacobsen, Elizabeth M. Prystas10.1200/jop.2006.2.4.149Journal of Oncology Practice

[21] A study on the adverse effects of anticancer drugs in an oncology center of a tertiary care hospital. Kirchi.c, azra afzal mounika reddy.seyed aamir ali aparna yerramilli, sanjeev sharma. International Journal of Pharmacy and Pharmaceutical Sciences. ISSN- 0975-1491 Vol 6, Suppl 2, 2014

[22] Side Effects of Chemotherapy among Cancer Patients in a Malaysian General Hospital: Experiences, Perceptions and Informational Needs from Clinical Pharmacists 2014Huan-Keat Chan, Sabrina Ismail10.7314/apjcp.2014.15.13.5305Asian Pacific Journal of Cancer Prevention

[23] Anti-emetics: American Society of Clinical Oncology Clinical Practice Guideline Update. 2017. Paul J. Hesketh, Mark G. Kris, Ethan Basch, Kari Bohlke, Sally Y. Barbour, Rebecca Anne Clark-Snow, Michael A. Danso, Kristopher Dennis, L. Lee Dupuis, Stacie B. Dusetzina, Cathy Eng, Petra C. Feyer, Karin Jordan, Kimberly Noonan, Dee Sparacio, Mark R. Somerfield, Gary H. Lyman10.1200/jco.2017.74.4789Journal of Clinical Oncology

[24] Guidelines for the control of nausea and vomiting with chemotherapy of low or minimal emetic potential Ian Olver, Rebecca A. Clark-Snow, Enzo Ballatori, Birgitte T. Espersen, Emilio Bria & Karin Jordan Supportive Care in Cancer volume 19, pages33-36(2011)

[25] Einhorn LH, Brames MJ. Emetic potential of daily oral etoposide. Support Care Cancer 2006;14:1262-1265.

[26] Evaluation of new anti-emetic agents and definition of antineoplastic agent emetogenicity—an update, 2004, Steven M. Grunberg, David Osoba, Paul J. Hesketh, Richard J. Gralla, Sussanne Borjeson, Bernardo L. Rapoport, Andreas du Bois, Maurizio Tonato 10.1007/s00520-004-0718-y, Supportive Care in Cancer

[27] Evaluation of new anti-emetic agents and definition of antineoplastic agent emetogenicity—state of the art 2010Steven M. Grunberg, David Warr, Richard J. Gralla, Bernardo L. Rapoport, Paul J. Hesketh, Karin Jordan, Birgitte T. Espersen10.1007/s00520-010-1003-xSupportive Care in Cancer

[28] Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implication 2005Olga Geling, Hans-Georg Eichler10.1200/jco.2005.04.022Journal of Clinical Oncology

[29] A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis 2007K. Jordan, A. Hinke, A. Grothey, W. Voigt, D. Arnold, H.-H. Wolf, H.-J. Schmoll10.1007/s00520-006-0186-7Supportive Care in Cancer

[30] Anti-emetic Efficacy of an Oral Suspension of Granisetron plus Dexamethasone and Influence of Quality of Life on Risk for Nausea and Vomiting 2005Karin Jordan, Axel Grothey, Thomas Kegel, Christian Fibich, Christoph Schöbert10.1159/000082523Oncology Research and Treatment

[31] Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist 2003Peter Eisenberg, Jazmin Figueroa-Vadillo, Rosalio Zamora, Veena Charu, Julio Hajdenberg, Alan Cartmell, Alberto Macciocchi, Steven Grunberg10.1002/cncr.11817Cancer

[32] Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron 2003R. Gralla, M. Lichinitser, S. Van der Vegt, H. Sleeboom, J. Mezger, C. Peschel, G. Tonini, R. Labianca, A. Macciocchi, M. Aapro10.1093/annonc/mdg417Annals of Oncology

[33] Comparative activity of anti-emetic drugs 2007Karin Jordan, Hans J. Schmoll, Matti S. Aapro10.1016/j.critrevonc.2006.08.003Critical Reviews in Oncology/Hematology

[34] Anti-emetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis 2007S.M. Grunberg10.1093/annonc/mdl347Annals of Oncology

[35] Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer After Moderately Emetogenic Chemotherapy 2005David G. Warr, Paul J. Hesketh, Richard J. Gralla, Hyman B. Muss, Jørn Herrstedt, Peter D. Eisenberg, Harry Raftopoulos, Steven M. Grunberg, Munir Gabriel, Anthony Rodgers, Norman Bohidar, George Klinger, Carolyn M. Hustad, Kevin J. Horgan, Franck Skobieranda10.1200/jco.2005.09.050Journal of Clinical Oncology

[36] Randomized, Double-Blind, Dose- Finding Study of Dexamethasone in Preventing Acute Emesis Induced by Anthracyclines, Carboplatin, or Cyclophosphamide: 200410.1200/jco.2004.09.040Journal of Clinical Oncology

[37] Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. Italian Group for Anti-emetic Research. 199810.1200/jco.1998.16.9.2937Journal of Clinical Oncology

[38] The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin—The Aprepitant Protocol 052 Study Group 2003Paul J. Hesketh, Steven M.

Grunberg, Richard J. Gralla, David G. Warr, Fausto Roila, Ronald de Wit, Sant P. Chawla, Alexandra D. Carides, Juliana Ianus, Mary E. Elmer, Judith K. Evans, Klaus Beck, Scott Reines, Kevin J. Horgan10.1200/jco.2003.01.095Journal of Clinical Oncology

[39] Addition of the neurokinin 1 receptor antagonist aprepitant to standard anti-emetic therapy improves control of chemotherapy-induced nausea and vomiting 2003Sergio Poli-Bigelli, Jose Rodrigues-Pereira, Alexandra D. Carides, Guoguang Julie Ma, Krista Eldridge, Anita Hipple, Judith K. Evans, Kevin J. Horgan, Francesca Lawson, 10.1002/cncr.11433Cancer

[40] Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for anti- emetic efficacy in high-dose cisplatin treatment 2006H.J. Schmoll, M.S. Aapro, S. Poli-Bigelli, H.-K. Kim, K. Park, K. Jordan, J. von Pawel, H. Giezek, T. Ahmed, C.Y. Chan10.1093/annonc/mdl019Annals of Oncology

[41] Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients 2005Peter Nygren, Kenneth Hande, Kevin J. Petty, Margaret Fedgchin, Kristien van Dyck, Anup Majumdar, Debbie Panebianco, Marina de Smet, Tuli Ahmed, M. Gail Murphy, Keith M. Gottesdiener, Veronique Cocquyt, Simon van Belle10.1007/s00280-004-0946-3Cancer Chemotherapy and Pharmacology

[42] Comparison of three protracted anti- emetic regimens for the control of delayed emesis in cisplatin-treated patients 1992Isabel Moreno, Rafael Rosell, Albert Abad, Agusti Barnadas, Joan Carles, Nuria Ribelles, Victoria Solano, Albert Font10.1016/0959-8049(92)90515- 4European Journal of Cancer

[43] Controlling delayed vomiting: double- blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. 1989M G Kris, R J Gralla, L B Tyson, R A Clark, C Cirrincione, S Groshen10.1200/jco.1989.7.1.108Journal of Clinical Oncology

[44] A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the *Suncus murinus* (house musk shrew) 2004Magdalena Kwiatkowska, LindaA. Parker, Page Burton, Raphael Mechoulam10.1007/s00213-003-1739-9Psychopharmacology

[45] Regulation of nausea and vomiting by cannabinoids, 2011Linda A Parker, Erin M Rock, Cheryl L Limebeer10.1111/j.1476-5381.2010.01176.xBritish Journal of Pharmacology

[46] Update on anti-emetics for chemotherapy-induced emesis 2005I. N. Olver10.1111/j.1445-5004.2005.00879.xInternal Medicine Journal

[47] anti-emetic placebo: Reduce adverse drug interactions between chemotherapeutic agents and anti-emetic drugs in cancer patients, 2008Zhongyi Zhang, Yong Wang, Yan Wang, Feng, Xu10.1016/j.mehy.2007.06.029Medical Hypotheses

[48] Premedication with H1 and H2 blocking agents reduces the incidence of postoperative nausea and vomiting 2004A.W. Doenicke, R. Hoernecke, I. Celik10.1007/s00011-004-0367-0Inflammation Research

[49] Radioreceptor Binding Profile of the Atypical Antipsychotic Olanzapine 1996Frank P Bymaster, David O Calligaro, Julie F Falcone, Richard D Marsh, Nicholas A Moore, Nicholas C Tye, Philip Seeman, David T Wong10.1016/0893-133x(94)00129-nNeuropsychopharmacology

[50] A phase II trial of olanzapine for the prevention of chemotherapy-induced

nausea and vomiting: A Hoosier Oncology Group study 2005Rudolph M. Navari, Lawrence H. Einhorn, Steven D. Passik, Patrick J. Loehrer, Cynthia Johnson, M. L. Mayer, J. McClean, Jake Vinson, W. Pletcher10.1007/s00520-004-0755-6Supportive Care in Cancer

[51] A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier oncology group study 2007Rudolph M. Navari, Lawrence H. Einhorn, Patrick J. Loehrer, Steven D. Passik, Jake Vinson, John McClean, Naveed Chowhan, Nasser H. Hanna, Cynthia S. Johnson10.1007/s00520-007-0248-5Supportive Care in Cancer.

[52] Treatment of Breakthrough and Refractory Chemotherapy-Induced Nausea and Vomiting 2015Rudolph M. Navari10.1155/2015/595894BioMed Research International

[53] Anti-emetics: American Society of Clinical Oncology Clinical Practice Guideline Update Summary 2017Paul J. Hesketh, Kari Bohlke, Mark G. Kris10.1200/jop.2017.026351Journal of Oncology Practice

[54] Medication Error Factors, Safety Guideline System, Flow of Drug Usage, and Code of Conduct to Prevent Medication Error, 2018, Arvidareyna Panca, Nikma Fitriasari, Wiwik Supartiwi 10.11594/bbrj.01.02.01, Bioinformatics and Biomedical Research Journal