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ADVERSE DRUG REACTION PROFILE OF CANCER PATIENTS ON CHEMOTHERAPY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

A monitoring program was carried out in Department of Radiotherapy and Oncology, Kasturba Hospital, Manipal, a tertiary care hospital in South India to monitor and assess the pattern of Adverse Drug Reactions (ADRs) in cancer patients receiving chemotherapy. Case records, drug charts, medical and nursing notes of patients receiving chemotherapy were reviewed and analyzed for presence of any ADRs. Laboratory results, patient notes, discussion with the doctors and patient interview served as the markers for ADRs. Five hundred eighty two suspected ADRs were reported in 387 patients during the study period. Common ADRs were fever, neutropenia, anemia, thrombocytopenia, peripheral neuropathy, hand foot syndrome, constipation, oral ulcers, blackening of nails, skin pigmentation, maculopapular rash, pustules, erythematous patch, scaling of body, hearing loss and ear pain. All patients developed type A reaction. Naranjo's algorithm showed all ADRs to be 'probable'. Only 1% ADRs were found to be definitely preventable. The study showed that chemotherapy has a high potential to cause ADRs. Thus, there is a need for vigilant ADR monitoring to prevent morbidity and mortality due to ADRs.

KEYWORDS: Adverse drug reaction, Tertiary care hospital, Chemotherapy, Type A reaction, Naranjo's algorithm.

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INTRODUCTION

Adverse drug reactions (ADRs) are any noxious, unintended and undesired effects of a drug which occur at doses normally used in man for prophylaxis, diagnosis or treatment of disease, or for the modification of physiological function. The safe use of medicine is an important issue and an ongoing ADR monitoring and reporting program can provide benefits to the organization, pharmacists, other health care professionals and more importantly to patients.[1] Following the thalidomide disaster of 1960 which reported increased frequency of birth defects (seal limbs) that left 10,000 babies disabled for life, monitoring centres were started world over.[2] ADRs have been implicated as a leading cause of considerable morbidity and mortality. The incidence of ADR varies with studies which show incidences ranging from as low as 0.15% to as high as 30%.[3] ADRs account for approximately 2.1% of hospital admissions, with 39.3% of them being life-threatening.[4] Elderly and hospitalized patients are reported to be more susceptible to ADRs than the adult population.[3] ADRs are identified as the fifth leading cause of death in USA with an estimated incidence of 6.7%. Of this 0.32% account for fatality among hospitalized patients.[5,6] The practice of cancer medicine has changed spectacularly in the past four decades, as curative treatments have been identified for a number of previously fatal malignancies such as testicular cancer, lymphomas and leukaemia. Chemotherapy is employed as part of a multimodal approach to the treatment of many tumors. Many of the adverse effects of antineoplastic drugs are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells. Common ADRs due to cancer chemotherapy are alopecia, nausea and vomiting, myelosuppression, haemorrhagic cystitis, mucositis, increased toxicity with impaired renal function, cardiac toxicity, hot flushes, electrolyte imbalance, deep vein thrombosis etc.[7] A recent study from a South Indian tertiary care teaching hospital has reported antineoplastic agents as the common class of drugs causing the ADRs accounting for a total of 21.8% of the reported ADRs. Compromising dose intensity of drug or by delaying the doses, ADRs can be minimized but it can greatly affect their efficacy.[8] In India, certain factors such as large number of patients, poor doctor-patient ratio, self medication, use of alternative systems of medicine, presence of counterfeit drugs and presence of highest number of drug combination products in the world leads to a higher incidence of ADRs. Thus it becomes mandatory to identify, understand, predict and ultimately reduce the burden of ADRs. Rising costs of patient care, increasing awareness of patients towards the untoward effects of the drugs and the rise in the frequency of cases of litigation against doctors and hospitals have made clinicians, hospital administrators and health care providers aware of the necessity to closely monitor adverse drug reactions.[9] The safety profile of cancer chemotherapy still remains a question. In India, ADR rates and incidences in relation to number of drugs prescribed or patients exposed have been assessed only in few survey and projects. With this background, the aim of this study was to study the pattern of ADRs and drugs implicated in local population, analyzing the characteristics of all ADRs, including the classes of drugs that most commonly cause ADRs, the causality of the drug causing the ADRs, the severity and preventability of each ADR.

MATERIALS AND METHODS

An intensive adverse drug reaction monitoring program was carried out in the department of Radiotherapy and Oncology, Kasturba Hospital, Manipal, a tertiary care hospital in South India from September 2011 to August 2013. The study was approved by institutional ethics committee. (IEC 169/2011). The investigator visited the department daily to check for the ADRs caused by chemotherapeutic agents. Case records, drug charts, medical and nursing notes of the patients were reviewed for the presence of any evidence of adverse drug reactions. Laboratory results, patient notes,

discussion with the doctors and patient interview served as the markers for ADRs. Patients who experienced ADR were followed from the day of reporting of an ADR until the discharge of patients to collect the updated and complete information. The collected data were documented in a separate ADR documentation form. Suspected ADRs were analyzed for various parameters. ADRs were classified as type A or type B based on Rawlins and Thompsons classification.[10] To assess the likelihood that the drug has caused the reaction, Naranjo's algorithm was used. As per this scale, an ADR can be definite, probable, possible or doubtful depending on the scores obtained. [11] Hartwig scale (Hartwig *et al*, 1992) was used to assess the severity of ADRs which categorizes the reported adverse drug reactions into different levels as mild, moderate or severe. [12] ADRs were categorized into definitely preventable, probably preventable and not preventable based on modified Schumock and Thorton scale. [13] All reported ADRs were studied in detail to understand the characteristics of ADRs based on patients' gender, onset of reaction, type of reaction (type A and B), drugs involved in causing ADR, various organ system affected, predisposing factors, management and outcome of ADRs.

Statistical analysis

Data was analyzed using descriptive statistics and results were expressed as percentage. Mean with 95% confidence interval (CI) was used to summarize the age of patients. Chi-square test was used to identify an association between the gender and age group of patients with ADRs. Values of $p < .05$ were considered to be statistically significant. All analyses were performed using SPSS version 16.

RESULTS

Out of 1026 new cancer patients who received chemotherapy during duration of 2 years, 387 (37.70 %) patients developed a total of 582 ADRs. Of 387 patients, 171 (44.19%) were male and 216 (55.81%) were female which showed that ADRs were more common in females. Mean age of patients was 50.85 ± 11.82 years (95% CI, 49.66-52.03). Incidence of ADRs was more in older adults. Table 1 shows the demographic characteristics of the patients.

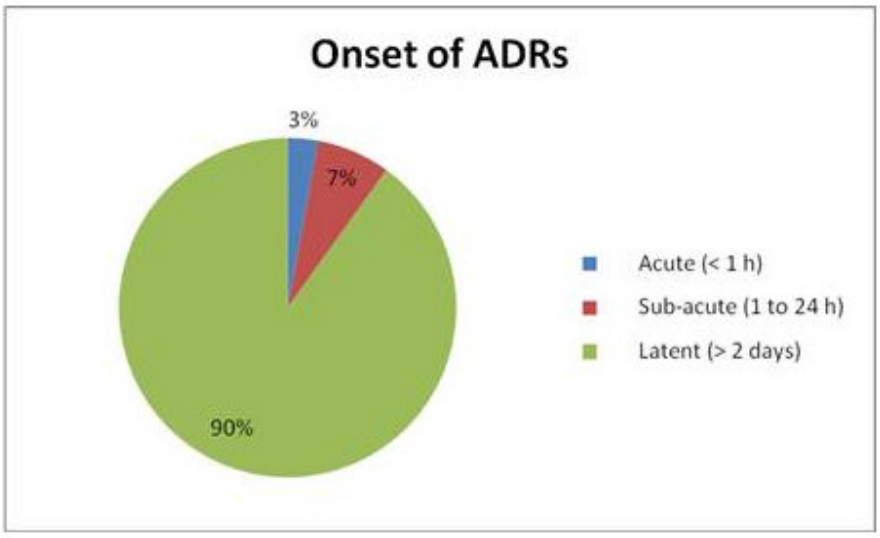
Table 1
Demographic characteristics of patients

Characteristics	Patients with ADR, n (%)
Gender	
Male	171 (44.19)
Female[a]	216 (55.81)
Age group	74 (19.12)
21-40	230 (59.43)
41-60[b]	81 (20.93)
61-80	2 (0.52)
>80	

ADR, adverse drug reaction
a. $\chi_1^2 = 0.323$, $P = 0.57$
b. $\chi_3^2 = 62.83$, $P = .001$

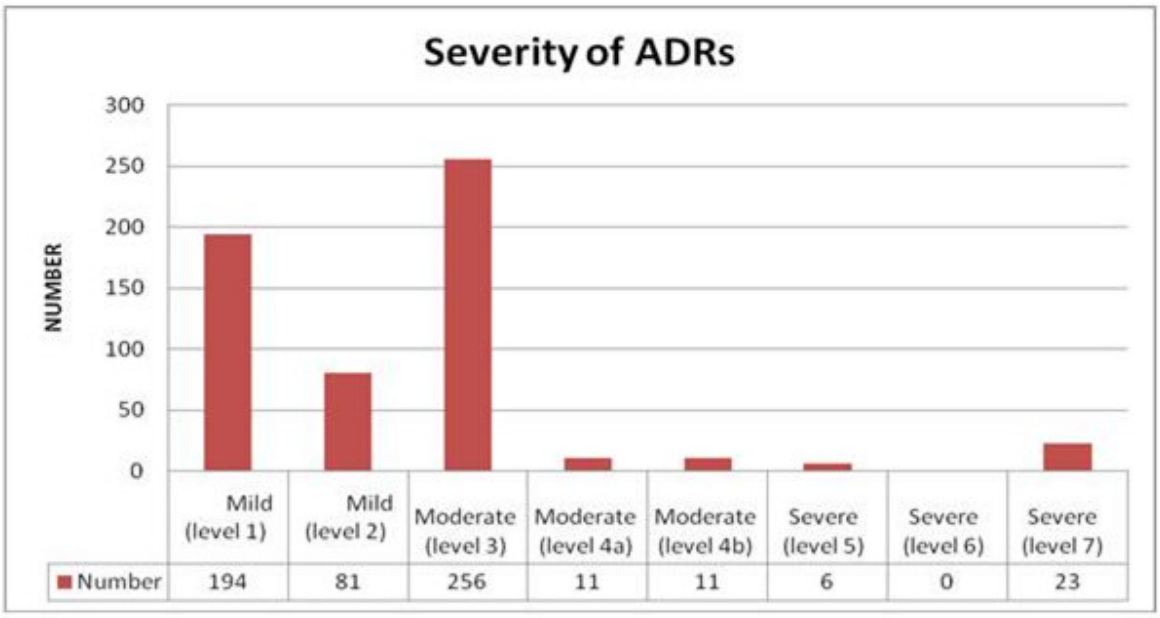
All reactions (100%) were of Type A. Causality assessment showed that all reactions were probable.

Figure 1
Pie chart showing the onset of ADRs



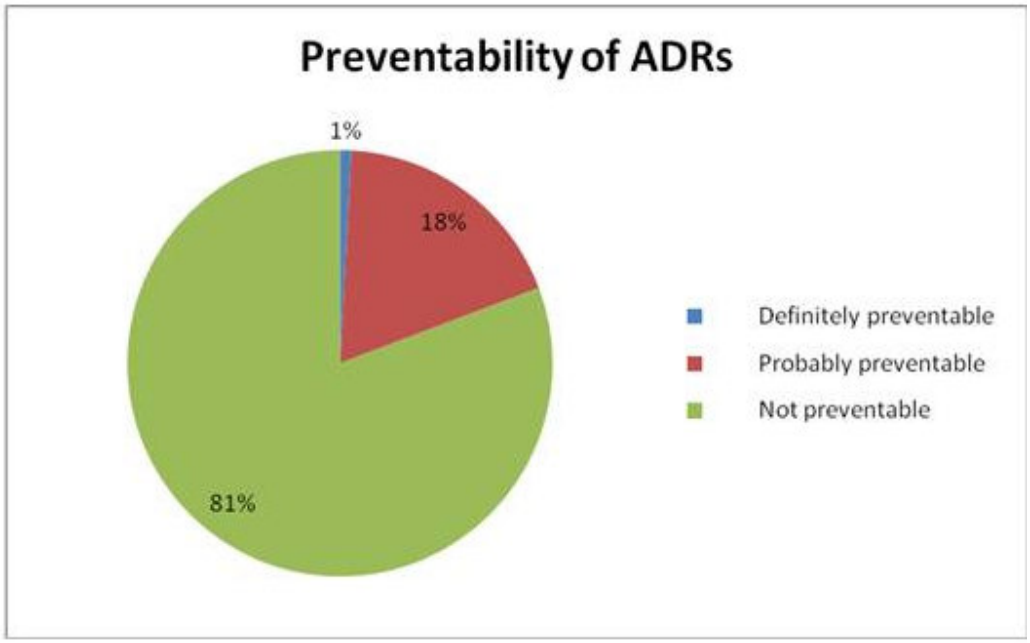
Most of the reported ADRs (90%) had latent onset followed by 7% sub-acute and only 3 % had an acute onset of reaction.

Figure 2
Graph representing the severity of ADRs



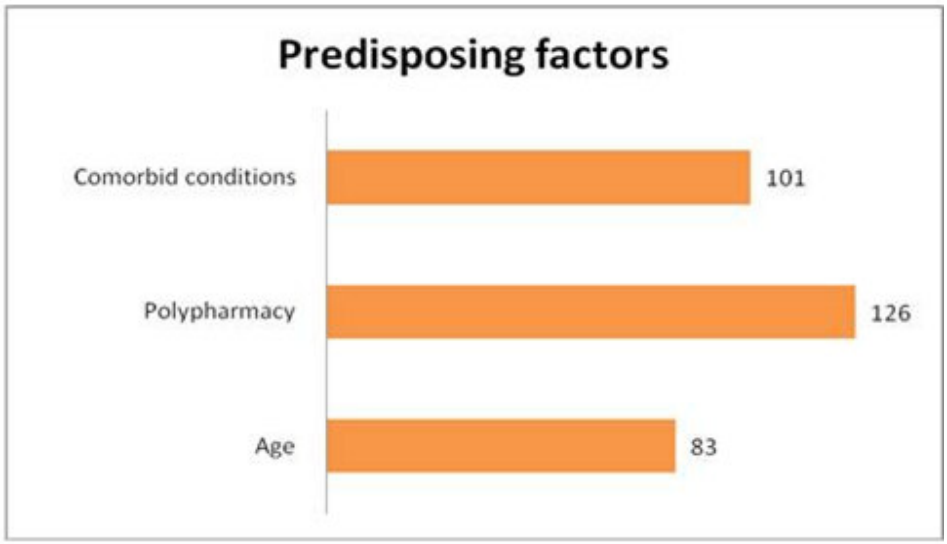
Moderate (level 3) type reaction was the most observed followed by mild (level 1) and mild (level 2). 23 ADRs (severe level 7) lead to the death of the patient. Moderate (level 4a, 4b) and severe (level 5) were less observed and there were no severe (level 6)ADRs.

Figure 2
Pie chart showing preventability of ADRs



Most of the ADRs were not preventable, some were probably preventable and very few were found to be definitely preventable.

Figure 3
Bar diagram representing the predisposing factors for ADRs



126 patients were on polypharmacy, 101 had comorbid condition and 83 patients were above 60 years of age. In some patients, more than one predisposing factor was observed.

Table 2
Drugs reported to cause ADRs (Total no. of ADRs = 582)

Individual drugs	No. of ADRs	Drug combinations	No. of ADRs
Cisplatin	56	Oxaliplatin + Capecitabine	27
Carboplatin	14	Docetaxel + Capecitabine	11
Oxaliplatin	5	Paclitaxel + Carboplatin	69
Melphalan	2	Doxorubicin + Bleomycin + Vinblastine + Dacarbazine	6
5-Flurouracil (5-FU)	15	Doxorubicin + Cyclophosphamide + 5-FU	27
Gemcitabine	7	Carboplatin + Pemetrexed	4
Capecitabine	52	Oxaliplatin + 5-FU	6
Vinblastine	3	Vincristine + Actinomycin D + Cyclophosphamide	4
Paclitaxel	50	Cisplatin + Etoposide	8
Docetaxel	13	Doxorubicin + Cyclophosphamide	56
Irinotecan	5	Bleomycin + Etoposide + Cisplatin	6
Bleomycin	3	5-FU + Cisplatin	4
Sorafenib	21	Epirubicin + Capecitabine + Oxaliplatin	17
Erlotinib	15	Doxorubicin + Vincristine + Cyclophosphamide	7
Sunitinib	7	Cisplatin + Gemcitabine	2
Lapatinib	2	Carboplatin + Gemcitabine	14
Geftinib	15	Cisplatin + Doxorubicin	4
Imatinib	2	Carboplatin + Etoposide	4
Lenalidomide	3	Doxorubicin + Ifosamide	3
Temozolomide	2	Gemcitabine + Erlotinib	7
Bortezomib	2	Doxorubicin + Cyclophosphamide + Docetaxel	1
Hydroxyurea	1		

Of the individual drugs causing ADRs, patients on cisplatin showed highest no. of ADRs followed by capecitabine and paclitaxel.
Of the drug combinations, patients on paclitaxel + carboplatin showed highest no. of ADRs followed by doxorubicin + cyclophosphamide.

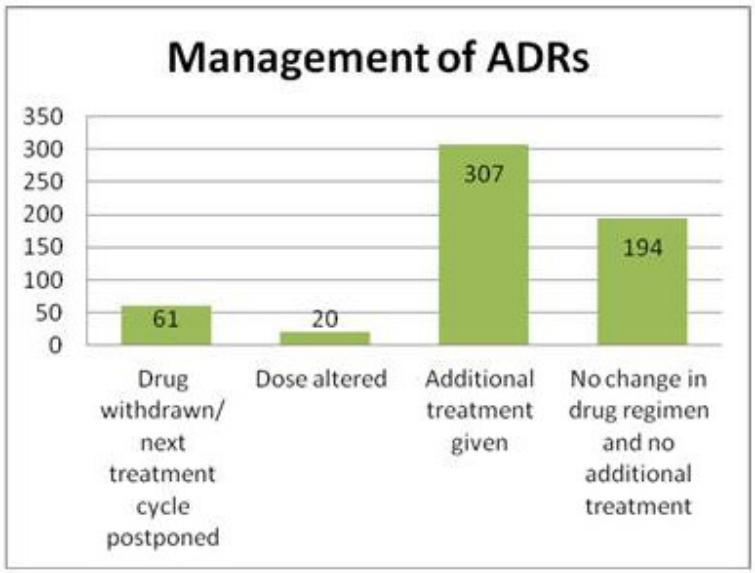
Table 3
ADRs and organ system affected

Organ system involved	Adverse drug reactions	No. of ADRs
Blood	Anemia	39
	Thrombocytopenia	69
	Neutropenia	42
	Leucopenia	45
	Febrile neutropenia	37
Cardiovascular system	Cardiomyopathy	4
CNS and PNS	Peripheral neuropathy	40
	Fever	7
Gastrointestinal system	Constipation	12
	Diarrhoea	27
	Oral ulcers	3
	Oral candidiasis	5
	Mucositis	11
	Paralytic ileus	3
	Gastritis	7
Musculoskeletal system	Pain in upper and lower limbs	6
	Severe weakness	9
	Pedal edema	4
	Swelling of great toe	2
	Pain over the right toe	2
Renal system	Urinary incontinence	2
	Urinary retention	2
	Hyponatremia	4
	Hypokalemia	3
Respiratory system	Breathlessness	9

Sensory system	Sensory neural hearing loss	4
	Tinnitus	7
	Ear pain	11
	Altered sensorium	2
Skin and appendages	Skin pigmentation	6
	Blackening of skin	15
	Skin rash with pustular eruptions	7
	Skin rashes	32
	Skin necrosis	5
	Maculopapular rash	5
	Erythematous patch	4
	Hand foot syndrome	45
	Rashes over the back and bilateral upper limbs	6
	Scaling of skin	7
	Sores	4
	Pustules over face and neck	3
	Exfoliative dermatitis	3
Others	Dysphagia	4
	Stomatitis	2
	Facial swelling	11
	Hypersensitivity reaction	5
Total		**582**

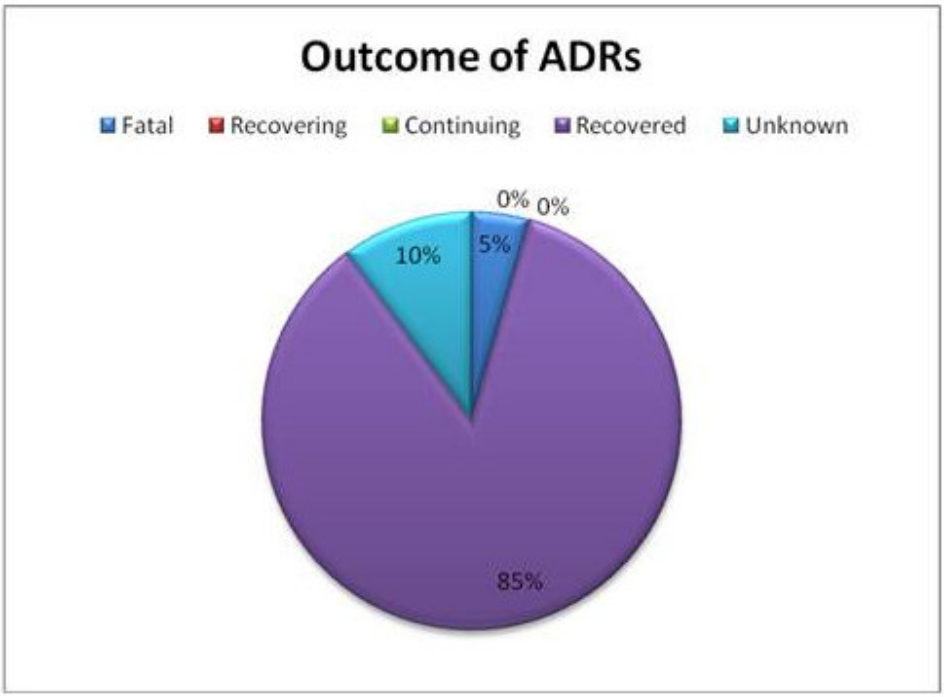
Commonly affected organ systems were blood, skin and appendages, Central Nervous System (CNS), Peripheral Nervous System (PNS) and gastrointestinal system. Chemotherapeutic agents commonly cause nausea, vomiting and alopecia hence, was not considered for this study.

Figure 5
Graph showing management of ADRs



52.7% of ADRs required additional treatment for their management.

Figure 6
Pie chart showing outcome of ADRs



Most of the patients recovered from ADRs after the completion of chemotherapy, 23 ADRs lead to death of the patient and outcome of 59 ADRs were unknown.

DISCUSSION

The incidence of ADRs in our hospital during the study period was 37.70% which is in contrast to the study conducted by Goyal et al (2014) which reported an incidence of 70% but similar to the study conducted by Mallik S et al (2007) with 40% incidence rate.[14, 15] The decreased incidence of ADRs reported in our hospital might be due to the exclusion of patients receiving concomitant chemotherapy and radiotherapy. Incidence of ADRs was more in females and Poddar et al (2009) also reported similar results.[8] However, it is in contrast to the study conducted by Prasad et al (2013) where the number of ADRs was more in male patients.[16]. All (100%) recorded ADRs were of probable causality with a score ranging from 5-8. Our study lacks rechallenge test (due to ethical reasons) which may be the reason for all ADRs to be probable. This is in contrast to the report by Prasad et al where 62% ADRs was probable, 31% ADRs was possible and about 7% was definite ADRs. [16] We found that 275 (47.25%) patients had mild reaction, 278 (47.77%) had moderate and 29 (4.98%) patients had severe type of reactions at different levels. This is similar to a report by Goyal et al (2014) where 53.26% reactions were of moderate type followed by mild 31.16% and severe 15.58%. [14] These ADRs could have been prevented to some extent. Based on modified Schumock and Thorton scale, it was found that 5 ADRs could have been prevented definitely and 107 ADRs could have been probably prevented but most of the ADRs (470) i.e. 80.75% of the ADR reported in our study were of not preventable category. This is analogous to the study conducted in Gujarat that showed 85.93% of ADRs are not preventable.[14]Some of the predisposing factors for ADRs were age (n = 83), polypharmacy (n = 126) and comorbid conditions (n = 101). ADRs were reported in 83 elderly patients (age> 60 years) in whom decreased metabolism and excretion of drug can lead to accumulation of drug thereby increasing the risk of causing ADRs.[16] Polypharmacy is common in older age group patients due to comorbid conditions which accounts for the increase in the risk of

ADRs. Several studies have shown a positive relationship between ADRs and polypharmacy.[18, 19] Cisplatin, Carboplatin, Paclitaxel, Capecitabine, Doxorubicin, Cyclophosphamide and 5-FU accounted for majority of the ADRs. This is probably due to the effect of alkylating agents and platinum analogs that interfere with DNA synthesis and function. They are not cell cycle specific and the adverse effects associated with these drugs are generally dose-related and occur primarily in rapidly growing tissues such as bone marrow, gastrointestinal tract, mucosal cells and the reproductive system. Antimetabolites like 5-FU and capecitabine mainly acts by inhibiting thymidylate synthase, which results in alteration in RNA processing and subsequently leads to inhibition of DNA synthesis and function. [20, 21] This may be the reason for more ADRs on bone marrow and buccal mucosa. This finding is consistent with the study conducted by Poddar et al where alkylating agents and antimetabolites contributed to 80% of the ADRs. [8] We have seen more haematological reactions (39.90%) which are probably due to the non-selective action of the anticancer drugs. They damage the rapidly dividing cells of the bone marrow along with the cancerous cells that causes bone marrow suppression leading to anemia, leucopenia, neutropenia and thrombocytopenia. Hand foot syndrome is commonly seen with capecitabine which require decrease in dose or stopping of therapy.[22] A study conducted by Llopis-Salvia et al (2010) showed an incidence of 71.4% haematological ADRs, mainly neutropenia and 11.4% gastrointestinal ADRs due to anticancer drugs. [21] Another recent study reported the overall frequency of neurological and cutaneous ADRs to be 5.9% and 5.63% respectively. [23, 24] We have also observed a similar pattern of ADRs. Fig.7, 8 and 9 shows some ADRs affecting skin and appendages.

Figure 7
Maculopapular rash, pustules & erythematous patch

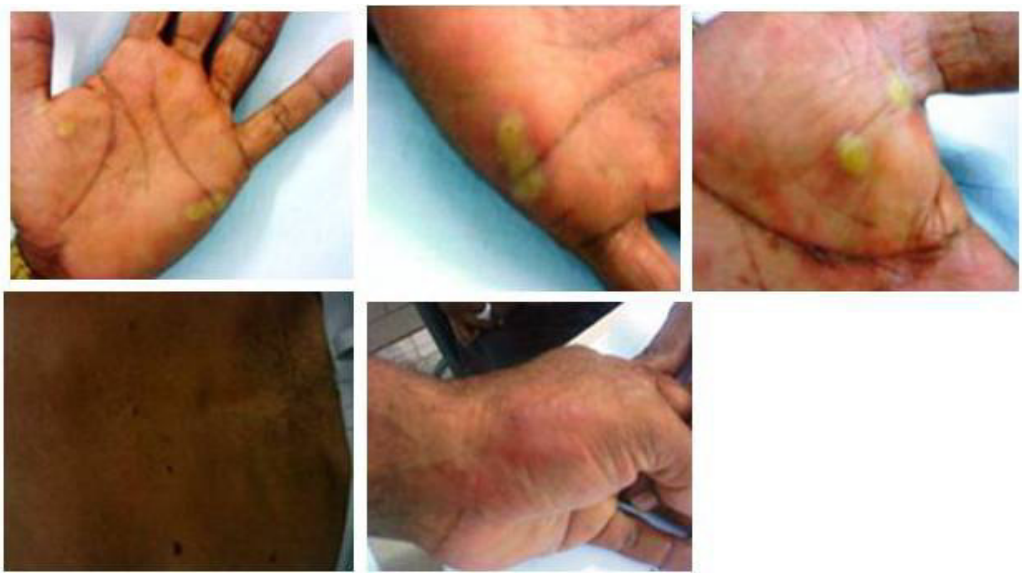


Figure 8
Necrosis

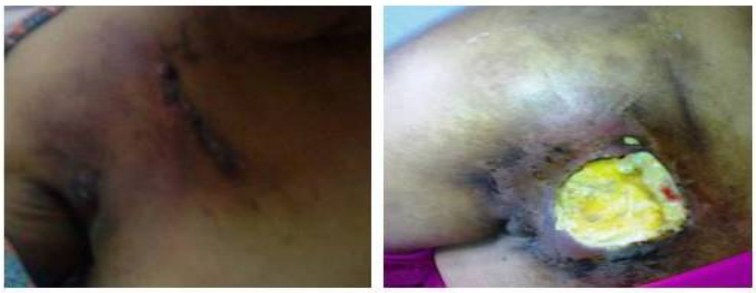
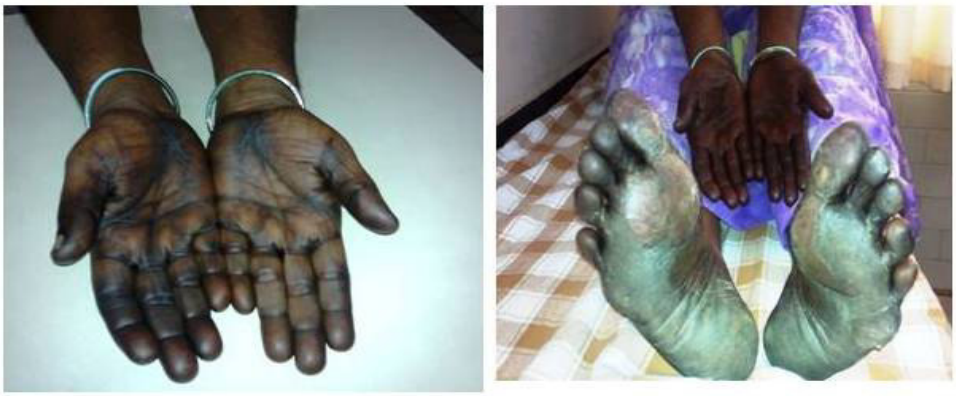


Figure.9
Hand Foot Syndrome



The ADRs were managed by multiple approaches. 11% ADRs required the chemotherapeutic agent to be withdrawn and the next chemotherapy cycle was postponed, 3% the dose was altered, 53% cases required additional treatment and in 33% ADRs there was no change in drug regimen and no additional treatment was given. This management strategy resulted in an outcome of 23 (4%) fatal episodes, 323 patients with a total of 500 ADRs recovered completely over a certain period of time. The outcome of 59 ADRs in 41 patients was unknown.

CONCLUSION

Since cancer chemotherapy has a high potential to cause ADRs, measures need to be put into place to reduce the physical, emotional and economic burden on the patient due to ADRs. Modification of dose of the drug and appropriate treatment measures should be implemented to further improve the benefit: harm ratio of the drugs. Therefore, there is a need for vigilant ADR monitoring to decrease morbidity and mortality due to ADRs which requires further studies on large populations.

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