Original Article

Pharmacology

A comparative assessment of the ADR profile in various anti-cancer regimens excluding gastro-intestinal and haematological toxicity at a tertiary care centre.

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ABSTRACT

This study compared the adverse drug reaction (ADR) profile in various anti-cancer regimens in 55 patients who attended a tertiary care centre. The adverse drug reactions which are caused by anti-cancer agents are common and they may be enhanced when the drugs are used in combinations. The cases which conformed to the inclusion criteriae were selected and the details were noted in a proforma, which were then statistically analyzed.

The results which were obtained, showed that the ADRs were common, but that they occurred in a similar frequency as in other study groups and that the severity grade was low. The counter measures to tackle the adverse reactions were also effective, leading to a hundred percent survival through the six cycles and the two year survival, which in itself spoke volumes about the ADRs. These findings were in tune with the findings of various researchers in the field of anti cancer toxicity profiles.

The incidence of the neurotoxicity, the dermatological adverse effects and other miscellaneous ADRs was frequent, but not of high severity.

Key Words: Anti-cancer, Adverse Drug Reaction, Compliance, Neurotoxicity, Dermatological Manifestation, Comparision of Regimen, Cancer Regimen

INTRODUCTION

Cancer is one of the major causes of mortality in the modern world, both in the developing and the developed countries. The research work which is being done on cancer takes time and meticulous documentation.

Cancer is no more spells doom for the patients, with the use of a combination of therapies.

The advent of a multimodal approach including chemotherapy, radiation, surgery and gene therapy have brought down the cancer death. Cancers are very much amenable to therapy, if they are diagnosed, early. In fact, some may be cured i,e, choriocarci noma, breast and teslicular tumours and lymphomas [1,2].

Anti-cancer drugs have been used to treat noncancerous diseases like-rheumatoid arthritis, organ transplants, sickle cell anaemias and psoriasis and as anti-infectives. Myelosuppression that is prolonged and cumulative, is produced by busulfan, leading to its use in the treatment of allogeneic bone marrow transplant cases [3].

The toxicity profiles of the anti-cancer drugs vary and the data has to be quantified in this regards. Hence, our study compared the toxicity profiles of 55 patients who had various types of malignancies. The gastro-intestinal toxicity and haematological toxicity form a major share of the anti-cancer ADRs; hence this aspect was discarded, and only all other ADR manifestations were considered. The major ADRs comprised of neurotoxicity, dermatological toxicity, nephrotoxicity, etc. [4,5]

PATIENTS AND METHODS

This was a prospective study which was conducted in the Department of Oncology, KMC, Attavar. Informed consent was taken from the patients who were included in the study.

INCLUSION CRITERIA

The study sample consisted of a total of 55 patients. Adult patients who were started on chemotherapy from July 1999 were included in the study. Patients who received chemotherapy for solid tumours, lymphomas and other types of cancers on an adjuvant or therapeutic basis were included in the study. Adult patients of any age group and of both sexes were included in the study.

EXCLUSION CRITERIA

Old cases i.e., the patients who were already on chemotherapy were not selected. Paediatric cases were not taken up for the study.

For the selected patients, the case history was made and an examination was done, the details of which were entered on special proformas and they were regularly followed up. The period of the study was 20 months. These details were entered into a spread sheet and the percentage distribution of each of the toxicities in the different grades were found out. A statistical analysis and a comparison study were done and the toxicities of the different regimens which could be statistically analyzed, were compared. Only 6 such regimens were compared in this study. A comparison between the base line values and the last cycle was made by using Wilcoxon's signed rank sum test, comparisons between the 6 cycles were done by using the Friedman test and comparisons within the regimens were done by using Fisher's exact test. Thus, the probability of significance and the p-value was found out with the help of these tests [6].

DISCUSSION

The main objective of our study was to assess the toxicity of various anti-cancer drugs by grading them as per the WHO guidelines and also to compare the toxicities of the different drug regimens.

This study was conducted on 55 diagnosed cases of various malignancies who received anti-neoplastic drugs in combination chemotherapy. Specific regimens which comprised of selected drugs were administered for individual malignancies according to the recommended schedules.

Because of ethical problems and technical difficulties, invasive procedures were not employed in this study, which limited the number of toxicities which were studied and so, only the clinically assessable toxicities were given prime importance.

Ca. bronchus was treated with a regimen of Etoposide and Cisplatin and the patient completed all the cycles of the chemotherapy, while experiencing only allergy, pigmentation, alopecia and renal toxicity (increase in blood urea and serum creatinine) as the adverse effects.

The VMCP regimen for multiple myeloma showed allergy, pigmentation, alopecia and a slight increase in blood urea and serum creatinine as the adverse effects.

The CMF, CC and FL regimens showed a higher degree of allergy in grade 0 as opposed to the other regimens.

The CMF, FL and the FC regimens showed raised blood urea in grade 1.

Most of the anti-cancer drugs damage the hair follicle. They produce either partial or complete alopecia, especially paclitaxel, cyclophosphamide, doxorubicin, vincristine, methotrexate and dactinomycin. Alopeica, nail changes, dermatitis, increased pigmentation and atrophy of the skin may be encountered3. Alopecia is also very common with the CMF regimen.

In our study, out of the 55 patients who were studied, only 12 (21.8%) patients were not affected by alopecia, whereas most of the patients, i.e., 43 (78.2%) were affected by alopecia. 13 (23.6%) patients showed grade 1 or mild hair loss and 30 (54.6%) showed grade 2, i.e., pronounced or total hair loss.

Other dermatological toxicities which were observed were allergy and hyper pigmentation (of the nails and skin).

Most of the patients were not much affected by allergy i.e., 41 (74.5%). Only 14 (25.5%) patients showed grade 1 allergy. The allergy was only mild.

Hyper pigmentation was seen in the nails and skin. A blackish discolouration of the skin and nails was observed. Most of the patients were affected with either grade 1, i.e., 13 (23.6%) or grade 2, 24 (43.6%) hyper pigmentation. 18 (32.7%) patients remained unaffected.

Diagnosis	Regimen	No. of pts.	Drugs	Dosage	Interval
Ca Breast	CMF	8	Cyclophosphamide Metho-trexate 5-fluorouracil	800-1000 mg/m^2 IV-d_1 50-65 mg/m^2 IV-d_1 750-1000 mg/m^2 IV-d_1	3 wkly/6 cycles
GIT & Hepatocellular	FL	6	5-fluorouracil Leucovorin	750 mg/m^2 IV-d_1-d_5 30 mg/m^2 IV-d_1-d_5	28 d/ 6 cycles
Head & Neck	FC	5	5-fluorouracil Cisplatin	500-1000 mg/m^2 IV-d_1-d_5 75-100 mg/m^2 IV-d_1	3 wkly / 6 cycles
Ca. Ovary	CC	5	Carboplatin or Cisplatin Cyclophosphamide	400 mg/m^2 IV-d_1 50-100 mg/m^2 IV-d_1-d_3 800-1000 mg/m^2 IV-d_1	3 wkly / 6 cycles
Ca. breast	CAF	4	Cyclophosphamide Doxorubicin 5-fluorouracil	800-950 mg/m^2 IV-d_1 60-90 mg/m^2 IV-d_1 750-950 mg/m^2 IV-d_1	3 wkly / 6 cycles
Ca stomach Ca pancreas	FAM	4	5-fluorouracil Doxorubicin Mitomycin	750-900 mg/m^2 IV-$_{1, 8,29,36}$ 40 mg/m^2 IV-d_1, d_{29} 10-15 mg/m^2 IV-d_1	Rpt every 56d.
Ostosarcoma	AC	2	Doxorubicin Cisplatin	70 mg/m^2 IV-d_1 50 mg/m^2 IV-d_1-d_3	3 wkly / 6 cycles
Ca breast	FEC	2	5-fluorouracil Epirubicin Cyclophosphamide	800 mg/m^2 IV-d_1 80 mg/m^2 IV-d_1 800 mg/m^2 IV-d_1	3 wkly / 6 cycles
Brain tumour	VLP	2	Vincristine Lomustine Procarbazine	2 mg/m^2 IV-d_1 40 mg/m^2 p.o.-d_1 100 mg/m^2 p.o.d_1-d_{10}	6 wkly / 6 cycles
Malignant fibrous histiocytoma	ID	1	Ifosfamide Doxorubicin	3.5 mg/m^2 IV-d_1-d_5 30 mg/m^2 IV-d_1-d_3	3 wkly / 6 cycles
Ca-Cervix	C	1	Cisplatin	90 mg/m^2 IV-d_1-d_2	28 d/ 6 cycles
NHL	CHOP	1	Cyclophosphamide Doxorubicin Vincristine Prednisolone	1200 mg/m^2 IV-d_1 70 mg/m^2 IV-d_1 2 mg/m^2 IV-d_1 20 mg/m^2 p.o.d_1-d_5	3 wkly / 6 cycles
NHL	COP	1	Cyclophosphamide Vincristine Prednisolone	700 mg/m^2 IV-d_1 2 mg/m^2 IV-d_1 20 mg/m^2 p.o.d_1-d_5	3 wkly / 6 cycles
Ca Breast	CXF	1	Cyclophosphamide Mitoxantrone 5-fluorouracil	800 mg/m^2 IV-d_1 20 mg/m^2 IV-d_1 750 mg/m^2 IV-d_1	3 wkly / 6 cycles

[Table/Fig-1a]: Heading missing

Severe skin reactions like atrophy of the skin were not seen in our study.

Renal tubular damage was the major toxic symptom which was associated with cisplatin, streptozocin and high-dose methrotrexate therapy. Acute haemorrhagic cystitis could complicate the cyclophasphamide and ifosfamide therapies [2].

In our study, the blood urea levels were increased in a majority of the patients. Out of the 55 patients who were treated with different anti-cancer drugs, 39 (70.9%) showed an increase in the blood urea levels. Out of the total patients who were affected, 32 (58.2%) patients had grade 1 severity, 5 (9.1) patients had grade 2 severity and 2 patients (3.6%) showed grade 3 severity. Only 16 (29.1%) patients remained unaffected.

The serum creatinine levels were also increased. All the 55 patients (100%) were affected, out of which 39 (70.9%) had grade 1 severity and 16 (29.1%) had grade 2 severity. No patient remained unaffected. Nephrotoxicity was present, even though the patients received diuretics, hydreation and MESNA. The blood urea and serum creatinine levels showed a significant difference ($p<0.005$) before and after the chemotherapy. No other toxicities like haemorrhagic cystitis, urinary incountinence, dysuria and renal failure were observed in this study.

The mean body weight of the patients decreased at the end of 6 cycles of chemotherapy. The reasons for this may be the progression of the disease, the cytotoxic effects of the drugs, and also decreased food intake due to anorexia, nausea and vomiting.

Neurological dysfunction of several types was seen in patients who received cisplatin. A peripheral neuropathy has been described, primarily distal and sensory, with parasthaesias of the hands and feet, abnormal vibration and position sense and diminished light touch. Studies which were conducted in the affected patients were abnormal. Cisplatin can produce ototoxicity with a high frequency of hearing loss, tinnitus, and even deafness.

Other toxicities which were noted during the chemotherapy were neurotoxicity in the form of mild parasthaesia, a tingling sensation in the extremities and tinnitus. These were seen in patients who received regimens containing cisplatin. This can be attributed to the toxicity of the platinum co-ordination complex, cisplatin in our study.

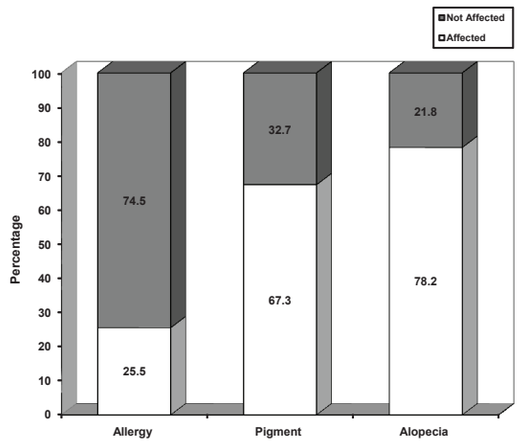
Pulmonary damages were found in occasional patients after the treatment with cyclophosphamide.

Diagnosis	Regimen	No. of pts.	Drugs	Dosage	Interval
Ca Bronchus	EC	1	Etoposide Cisplatin	200 mg/m^2 IV-d_1-d_3 50 mg/m^2 IV-d_1	3 wkly/6 cycles
Ca. Rectum	F	1	5- fluorouracil	5-fluorouracil	28d/6 cycles
Anoretcal ca	FMM	1	5-fluorouracil Mitomycin Mitoxantrone	500 mg/m^2 IV-d_1-d_5 10 mg/m^2 IV-d_1 20 mg/m^2 IV-d_1	3 wkly/6 cycles
Ca.Ceacum	FLe	1	5- fluorouracil Levamisole	750 mg/m^2 IV-d_1-d_5 for 1st cycle, then wkly 150 mg/m^2 -p.o. -d_1-d_3 every other week	Weekly
Naso-pharyngeal Ca.	MICE	1	Mesna Ifosfamide Cisplatin Etoposide	400 mg/m^2 IV-d_1-d_5 2 mg/m^2 IV-d_1-d_5 50 mg/m^2 IV-d_3-d_5 200 mg/m^2 IV-d_1-d_5	3 Wkly/6 cycles
Ca. ureter	M-VAC	1	Methotraxate Vinblastine Doxorubicin Cisplatin	45 mg/m^2 IV-d_1 4 mg/m^2 IV-d1-d_2 45 mg/m^2 IV-d1-d_2 100 mg/m^2 IV-d_2	2d/15d/6cy
Ca. lung	MIME	1	Mesna Ifosfamide Mitomycin Etoposide	400 mg/m^2 IV-d_1-d_3 2 mg/m^2 IV-d_1-d_3 10 mg/m^2 IV-d_2 200 mg/m^2 IV-d_1-d_3	3 Wkly/6 cycles
Multiple Myeloma	MP	1	Melphalan Prednisolone	5 mg/m^2 p.o. -d_1-d_4 20 mg/m^2 0\p.o.-d_1-d_3	6 wkly
Ca. breast	VAC/ VadrC	1	Vincristine Doxorubicin Cyclophosphamide Actinomycin-D	2 mg/m^2 IV 70 mg/m^2 IV 700 mg/m^2 IV 1.5 g/ m^2 IV-d_1 20 mg/m^2 p.o.-d_1 -d_4	3 Wkly/6 cycles
NHL	VCAP	1	Vincristine Cyclophosphamide Doxorubicin Prednisolone	2 mg/m^2 IV-d_1 800 mg/m^2 IV-d_1 60 mg/m^2 IV-d_1 20 mg/m^2 p.o.-d_1 -d_4	3 Wkly/6 cycles
Multiple myeloma	VMCP	1	Vincristine Melphalan Cyclophosphamide Prednisolone	2 mg/m^2 IV-d_1 5 mg/m^2 p.o.-d_1 -d_4 600 mg/m^2 IV-d_1 10 mg/m^2 p.o.-d_1 -d_4	3 wkly/6 cycles
NHL	MINE	1	Mesna Ifosfamide Mitoxantrone Etoposide	400 mg/m^2 IV-d_1 -d_3 2 g/m^2 IV-d_1-d_3 20 mg/m^2 IV-d_1 100 mg/m^2 IV-d_1 -d_3	3 wkly/6 cycles

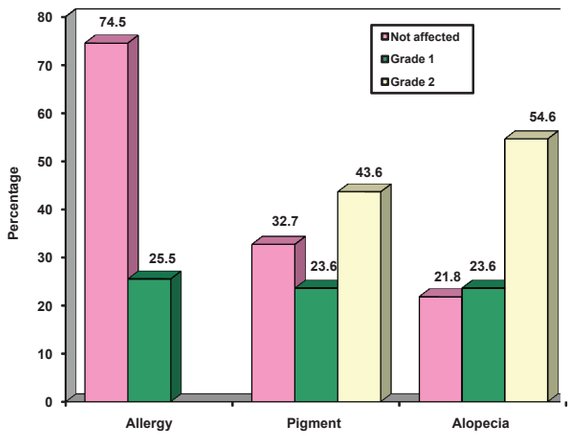
[Table/Fig-1b]: Heading missing

SYSTEM		% of ADR
Dermatology	Alopecia Allergy Hyper pigmentation	78.2% 74.5% 67.3%
CVS		2%
Metabolic		2%
Reproductive		2%
Renal	Increased blood urea Increased serum creatinine	70.9% 100%
Respiratory		5%
Neurotoxicity	Paraesthesia, Numbness	2%

[Table/Fig-2]: Adr Pertaining To Systems (Excluding Git And Haematology)



[Table/Fig-3]: Percentage distribution of dermatological toxicities.



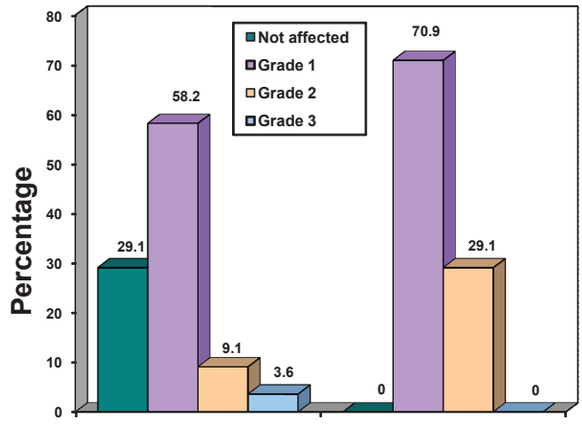
[Table/Fig-4]: Percentage distribution with grading of dermatological toxicities.

REGIMEN	BLOOD UREA				S. CREATININE		n
	GO	GI	G2	G3	G1	G2	
CMF	3	5			6	2	8
FL	1	4	1		5	1	6
CC	1	3	1		3	2	5
FC		4		1	5		5
CAF	3	1			2	2	4
FAM	1	3			3	1	4
AC		2			2		2

Contd....

REGIMEN	BLOOD UREA				S. CREATININE		n
	GO	GI	G2	G3	G1	G2	
FEC		1	1		2		2
VLP	1	1			2		2
C				1	1		1
CHOP		1				1	1
COP						1	1
CXF	1					1	1
EC		1			1		1
F	1				1		1
FMM		1			1		1
FLe	1					1	1
ICE			1		1		1
ID	1					1	1
M-VAC		1				1	1
MIME	1				1		1
MP	1					1	1
MINE						1	1
VAC/ VADRC		1				1	1
VCAP		1			1		1
VMCP		1			1		1
TOTAL N %	16 29.1	32 58.2	5 9.1	2 3.6	39 70.9	16 29.1	55 100

[Table/Fig-5]: Percentage Distribution and grading of renal toxicities in different regimens.



[Table/Fig-6]: Percentage distribution with grading of renal toxicities.

Few patients who were on the CC and CMF regimens showed milder forms of respiratory problems (cough and dyspnoea). This may be due to the cyclophoshamide component in those regimens.

Electrolyte disturbances like hypomagnesaemia, hypocalcaemia, hypokalaemia and hypophospataemia, etc have been discussed in the literature, but in this study, it was not possible to estimate all these criteriae routinely because of technical reasons.

Liver function tests did not show any statistically significant difference before and after the chemotherapy. Hence, in our study, no hepatotoxicity was observed due to the administration of the anti-cancer drugs.

CONCLUSIONS

This study noted the ADR profile in 55 patients who took various anti-cancer regimens along with radio therapy. The incidence of the drug reaction was very common, but of low severity, according to the WHO ADR grading system. This was also reflected in other such studies across the world. Hence, effective counter measures and a low incidence of mild ADR leads to a better compliance and an enhanced survival rate.

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