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COMPARATIVE STUDY ON EFFICACY AND TOXICITY OF DIFFERENT DOSES OF GEMCITABINE IN HEAD, NECK AND CERVICAL CANCER

Shibi Mary Thomas [1], Dr. Sirisha.S[2], Beny Baby [3], Narmada Sambashivam[4]

[1, 2, 3]Department of Pharmacy Practice, Karnataka College of Pharmacy, Bangalore, Karnataka, India.
[4]Department of Pharmacy Practice, KM College, Madurai, Tamilnadu, India.

ABSTRACT The purpose of this study was to determine the comparative study on efficacy and toxicity of different doses of Gemcitabine in head, neck and cervical cancers. Patients attending medical oncology unit, diagnosed as head and neck cancer patients based on biopsy, CT scan, cervical cancer diagnosis based on pap smear, ultra sound abdomen, urine examination and biopsy were studied. A total of 20 patients were included in the study, patients in stage III cancer were given Gemcitabine 200mg/week and stage I & II cancer patients were given Gemcitabine 100mg/week as radio sensitizer and this patients received radiotherapy. Size of tumour was observed every week to access the response to treatment. Patients were also observed for adverse drug reactions such as vomiting, diarrhoea, leukaemia, Mucositis. From this study, it can be concluded that Gemcitabine 200mg was comparatively more toxic than Gemcitabine 100mg whereas efficacy was more for Gemcitabine 200mg.

KEY WORDS: *Cervical cancer, Concurrent chemo radiotherapy, Gemcitabine, Oncology*.

INTRODUCTION

Cancer is a group of disease arising in all tissues composed of potentially dividing cells. Cancer can affect any of the body functioning system. The most common cancers in men are head and neck cancer, lung cancer, leukemias, lymphomas and colorectal cancer .In women, breast cancer, cancer of cervix, ovary, leukemias and lymphomas are the common cancers found. Neoplasia literally means "new growth". In Greek, Oncos means, tumor. So oncology is the study of tumors or Neoplasms.

Cervical cancer is the most frequent gynaecological cancer in women in many undeveloped and developing countries. The peak age of developing cervical cancer is 47yrs.Studies are going on in various parts of the world in the chemo radiotherapy in which Gemcitabine is used as radio sensitizer . Gemcitabine can be useful to make chemo radiotherapy as the standard treatment for Head, neck and cervix cancer patients.

Gemcitabine (dFdc) is a new anticancer nucleoside that is an analog of deoxycytidine. It is a prodrug and,once transported into the cell, must be phosphorylated by deoxycytidinekinase to an active form .Both Gemcitabine diphosphate (dFdcTP) and Gemcitabine triphosphate (dFdcTP) inhibit process required for DNA synthesis .Incoporation of dFcTP into DNA is the major mechanism by which Gemcitabine causes cell death .After incorporation of Gemcitabine, nucleotide on the end of the elongating DNA strand ,one more deoxy nucleotide is added and, therefore the DNA polymerases are unable to proceed. This action ("MASKED TERMINATION") apparently locks the drug into DNA as the proofreading enzymes, are unable to remove Gemcitabine from this position. Furthermore, the unique actions that Gemcitabine metabolites exert on cellular regulatory process serve to enhance the overall inhibitory activities on cell growth. This interaction is termed "Self potentiation" and is evidenced in very few other anticancer drugs.

MATERIALS AND METHODS

Site of the Study

The study was carried out at Meenakshi mission hospital and research Centre in Tamil Nadu. A total of 20 patients selected in the study, patients in stage III cancer were given Gemcitabine 200mg/wk and stage I & II were given Gemcitabine 100mg/wk as radio sensitizer and patients also received radiotherapy. Lab investigations such as Hb, TC, RBC, liver function test, serum creatinine, blood sugar were done before initiation of chemo radiotherapy and repeated every week till the scheduled cycles were completed.

Size of tumor was observed every week to ascess the response to treatment .patients were also observed for adverse drug reactions of drug such as vomiting,diarrohea,eukopenia,mucosities.

TREATMENT PROCEDURE

Gemcitabine 200mg or 100mg mixed in 200ml normal saline injection and given IV over 1 h period. It was decided to give 50Gy/day in 25 sittings for stage I &II .60Gy radiation 2 Gy/day in 30 sittings for stage III &IV patients .on the first day radiation is given ,patients are asked to come on 3rd day for chemotherapy. Next day radiation is given. Therefore a patient gets 100mg of Gemcitabine or 200mg in a week and Gy units of radiation in week.

RESULTS AND DISCUSSION

In the 100 mg Gemcitabine group consist of 10 patients, 3 of them were females and 7 were males .Out of this 8 (80%) were head and neck cancer patients and remaining 2(20%) were cervical cancer patients.

In the 200 mg Gemcitabine group, out of 10 patients, 6 were females and 4 were males' .In these 3 patients belonged to head and neck cancer category and remaining 7 were having cancer of cervix. Patients in Gemcitabine 200 mg were scheduled to receive 6 cycles and all of the 10 patients completed 6 cycles. Patients who received Gemcitabine 200mg as radio sensitizer were scheduled to receive 6 cycles. But they could complete only 2 cycles. Gemcitabine chemotherapy had to be compulsorily stopped because of very severe unmanageable toxicity such as Diarrhoea of Grade 2 and Grade 3.

TUMOR RESPONSE

Out of 10 patients in Group 1(100mg Gemcitabine) 3 patients (30%) achieved complete response and 7 patients (70%) showed partial response. Out of 10 patients in group 1(200mg Gemcitabine) 8 patients (80%) achieved complete response and 2 patients showed partial response.

Cycles	No of patients (100mg) (%) G0	No of Patients (%)GI	No of Patients (%)GII	No of Patients (%)GIII	No of Patients (200mg) (%) G0	No of Patients (%)GI	No of Patients (%)GII	No of Patients (%)G III
I	80 8/10	20 2/10	0 0/10	0 0/10	0 0/10	20 2/10	60 6/10	20 2/10
II	80 8/10	2O /10	0 0/10	0 0/10	0 0/10	10 1/10	80 8/10	10 1/10
III	70 7/10	30 3/10	0 0/10	0 0/10	Chemotherapy Discontinued			
IV	60 6/10	40 4/10	0 0/10	0 0/10				
V	50 5/10	30 3/10	20 2/10	0 0/10				
VI	50 5/10	40 4/10	10 1/10	0 0/10				

Table1: Incidence of Diarrhoea and the percentage of patients affected in different cycles of chemotherapy with 100mg &200mg Gemcitabine.

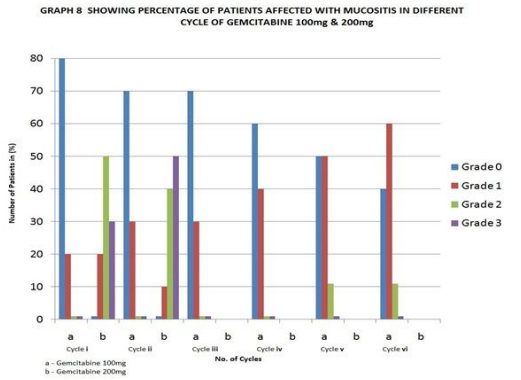

Figure 1: Graph showing percentage of patients affected with diarrhoea in different cycle of Gemcitabine 100 mg and 200 mg.

Cycles	No. of patients (100mg) % G0	No. of Patients % GI	No. of Patients % GII	No. of Patients % GIII	No. Of patients (200mg) % G0	No. of Patients % GI	No. of patients % GII	No.of Patients % GIII
I	80 8/10	20 2/10	0 0/10	0 0/10	0 0/10	20 2/10	50 5/10	30 3/10
II	70 7/10	30 3/10	0 0/10	0 0/10	0 0/10	10 1/10	40 4/10	50 5/10
III	70 7/10	30 3/10	0 0/10	0 0/10				
IV	60 6/10	40 4/10	0 0/10	0 0/10	Treatment Discontinued			
V	50 5/10	50 5/10	10 1/10	0 0/10				
VI	40 4/10	60 6/10	10 1/10	0 0/10				

Table 2: Incidence of Mucositis reaction and the percentage of patients affected in different cycles of chemotherapy with 100mg and 200mg Gemcitabine.

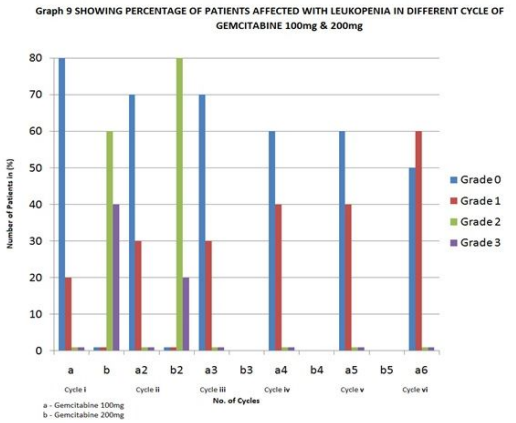

Figure 2: Graph showing percentage of patients affected with mucositis in different cycle of Gemcitabine 100 mg and 200 mg.

Grade 0 -Without Diarrhoea

Grade I - Diarrhoea lasting for< 3 days

Grade II –Diarrhoea lasting for 4 to 13 days

Grade III –Diarrhoea lasting for>14 days

Out of 10 patients receiving (100mg),8 patients showed G-0(80%) toxicity,2 patients showed G-1 (20%)toxicity in the 1st cycle:8 patients showedG-0 (80%) toxicity,2 patients G-I(20%) toxicity in 2nd cycle:7 patients showedG-0(70%)toxicity,3 patients showed G-I(30%) toxicity in 111 cycle:6 patients showed G-0(60%) toxicity,4 patients showed G-I(40%)toxicity in the 4th cycle:5 patient showed G-0(50%)toxicity,3 patient showedG-1(30%)toxicity,2 patient showed G-II(20%)toxicity in the 5 th cycle;5 patient showed G-0 (50%)toxicity,4 patients showed G-I(40%)toxicity, patient showed G-II(10%)toxicity in the 6th cycle.

Out of 10 Patients receiving(200mg),2 patients showed G-I(20%)toxicity,6 patients showed G-1(20%)toxicity,6 patients showed G-II(60%)toxicity,2 patients showed G-III(20%)in the 1st cycle;1 patient showed G-I(10%)toxicity,8 patients showed G-II(80%)toxicity,1 patient showed G-III(10%) toxicity, in the second cycle.

Cycles	No. of patients (100mg) % G0	No. of Patients % GI	No. of Patients % GII	No. of Patients % GIII	No. Of patients (200mg) % G0	No. of Patients % GI	No. of patients % GII	No.of Patients % GIII
I	80 8/10	20 2/10	0 0/10	0 0/10	0 0/10	20 2/10	50 5/10	30 3/10
II	70 7/10	30 3/10	0 0/10	0 0/10	0 0/10	10 1/10	40 4/10	50 5/10
III	70 7/10	30 3/10	0 0/10	0 0/10				
IV	60 6/10	40 4/10	0 0/10	0 0/10		Treatment Discontinued		
V	50 5/10	50 5/10	10 1/10	0 0/10				
VI	40 4/10	60 6/10	10 1/10	0 0/10				

Table 3: Incidence of leukopenia and the percentage of patients affected in different cycles of chemotherapy with 100mg and 200mg Gemcitabine

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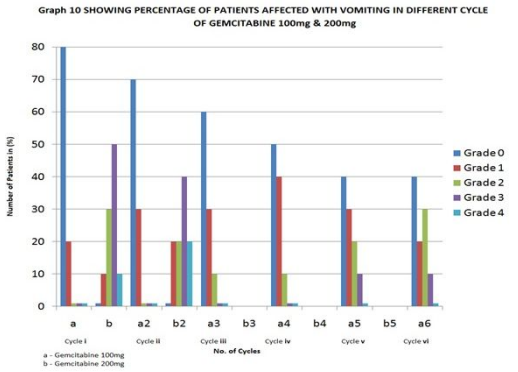

Figure 3: Graph showing percentage of patients affected with Leukopenia in different cycle of Gemcitabine 100 mg and 200 mg.

Grade 0 – without Mucositis

Grade I –Pain ulcers, erythema (or) mild soreness

Grade II –Painful ulcers, erythema (or) edema but still can eat

Grade III –Painful ulcers, erythema (or) edema and cannot eat.

Out of 10 patients, 8 patients showed G-0(80%)toxicity,2 patients showed G-1(20%)toxicity in the 1st cycle,7 patients showed G-0(70%)toxicity, 3 patients showed G-1(30%)toxicity in the 2nd cycle, 7 patients showed G-0(70%)toxicity, 3 patients show G-I(30%)toxicity in the 3rd cycle, 6 patients showed G-0(60%)toxicity, 4 patients showed G-I(40%)toxicity in the 4th cycle, 5 patients showed G-0(50%)toxicity, 5 patients showed G-I(50%)toxicity in the 5th cycle; 4 patients showed G-0(40%)toxicity, 6 patients

showed G-0(40%)toxicity, 6 patients showed G-I(60%)toxicity, 1 patients showed G-II(10%)toxicity in the 6th cycle.

Out of 10 patients receiving 2oomg,2 patients showedG-1(20%)toxicity,5 patients showedG-2(50%)toxicity,3 patients showed G-3(30%)toxicity in the 1st cycle;1 patients showed G-I(10%)toxicity,4 patients showed G-II(40%)toxicity,5 patient showed G-III(50%) toxicity, in the 2nd cycle.

No. of patients 100mg % G0	No. of patients % G1	No. of patients % GII	No. of Patients % GIII	No. of patients % GIV	No. of Patients % G0 200mg	No. of Patients % GI	No. of Patients % GII	No. of Patients % GIII
80 8/10	20 2/10	0 0/10	0 0/10	0 0/10	0 0/10	10 1/10	30 3/10	50 5/10
70 7/10	30 3/10	0 0/10	0 0/10	0 0/10	0 0/10	20 2/20	20 2/10	40 4/10
60 6/10	30 3/10	10 1/10	0 0/10	0 0/10	Treatment Discontinued			
50 5/10	40 4/10	10 1/10	0 0/10	0 0/10				
40 4/10	50 5/10	20 2/10	10 1/10	0 0/10				
40 4/10	20 2/10	30 3/10	10	0 0/10				

Table 4: Incidence of vomiting and the percentage of patients affected in different cycles of chemotherapy with 100mg Gemcitabine and 200mg Gemcitabine.

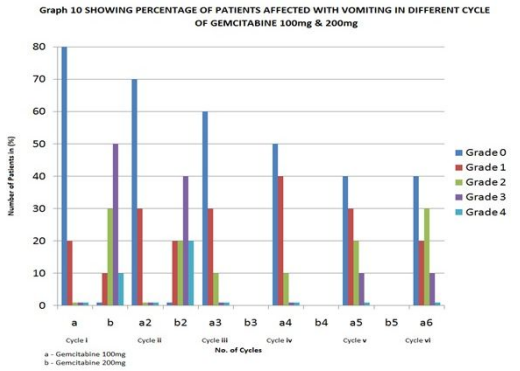

Figure 4: Graph showing percentage of patients affected with vomiting in different cycle of Gemcitabine 100 mg and 200 mg.

Grade-0 - 3000-4000/µl

Grade I - 2000-3000/µl

Grade II - 2000-1000/µl

Grade III - <1000/µl

Out of 10 patients,8 patients showed G-I(80%)toxicity,2 patients showed G-II(20%) toxicity in µpatients showed showed G-I(70%) toxicity,3 patients showed G-II(30%)toxicity in the 3rd cycle;6 patients showed G-I(60%)toxicity,4 patient showed G-II(40%)toxicity in the 4th cycle;6 patients showed G-I(60%)toxicity,4 patient showed G-II(40%)toxicity in the 5th cycle;5 patient showed G-I(50%)toxicity,5 patient showed G-II(50%)toxicity in the 6th cycle.

Out of 10 patients showed G-III(60%)toxicity,4 patient showed G-I(40%)toxicity in the 1st cycle;8 patient showed G-3(80%)toxicity,2 patient showed G-4(20%)toxicity in the 2nd cycle.

Grade 0 - without vomiting

Grade I - one episode in 24hrs

Grade II -2-5 episodes in 24hrs

Grade III -6-10 episodes in 24hrs

Grade IV-<10 episodes in 24hrs (or) required parenteral support.

Out of 10 patients,8 patients showed-0(80%)toxicity ,2 patients showed G-1(20%)toxicity in the 1st cycle;7 patients showed G-0(70%)toxicity,3 patients showed-1(30%)toxicity in the 2nd cycle;6 patients showed g-0 (60%)toxicity ,3 patients showed-1(30%) toxicity and 1 patient showed G-2 (10%) toxicity in the3rd cycle;5 patient showed G-0(50%)toxicity,4 patients G-0(40%)toxicity,3 patient showed G-1(30%)toxicity,2 patients showed G-2(20%)toxicity,1 patient showed G-III(10%)toxicity in the 4th cycle,4 patients showed G-0(40%) toxicity,2 patients showed-G-I(20%)toicity,3 patients showed-2(30%)toxicity,1 patient showed-3(10%)toxicity in the 6th cycle

Out of 10 patients ,1 patient showed G-I(10%)toxicity,3 patients showed G-II(30%)toxicity,5 patient showed G-III(50%)toxicity,1 patient showed-IV(10%)toxicity in the1st cycle.2 patients showed G-I(20%)toxicity,2 patients

showed G-II(20%),4 patient showed G-III(40%)toxicity and 2 patient showed G-IV(20%)toxicity in 2nd cycle.

CONCLUSION

Dose comparison study of Gemcitabine 100mg (Group-I) versus Gemcitabine 200mg (Group-II), 10 patients in each group with head and neck and cancer cervix patients showed:

80% complete response in Group –II patients and 30% complete response in Group 1 patients.-Grade II & Grade III toxicities of Diarrhoea, Mucositis, Leukopenia, vomiting were found in patients, therefore treatment had to be discontinued after 2 cycles.

Group 1 patients showed good tolerance and completed six cycles

From this study, it can be concluded that Gemcitabine 200mg was comparatively more toxic than Gemcitabine 100mg whereas efficacy was more for Gemcitabine 200mg.

REFERENCES

1) Englewood,coloredo: Gemcitabine, USPDI VOL1 Drug information for the healthcare professional update monographs micromedexinc 18th q`1`2october 1999.
2) Robinson.neoptasms text book of pathology.214:248.
3) Jones WB , mercergo et al .Early invasive carcinoma of cervic Gynecol oncol.51(1)26-32 1993.
4) Walter, miller, text book of radiotherapy radiation physics.13:231-235.
5) L Zhang ZZ Guan support for people with oral and Head and Neck Cancer journal of Oncology 2004ASCO annual meeting proceedings (post meeting edition) vol 22, no 148.
6) Gonzalez a Rivera Letal chemoradition with gemcitabine for cervical cancer In patients with renal failure.2004 sep15(8)76-6