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RESEARCH ARTICLE

A PROSPECTIVE STUDY OF EFFICACY AND SAFETY OF CONVENTIONAL CHEMOTHERAPY VS TARGETED THERAPY PLUS CHEMOTHERAPY IN RECURRENT AND METASTATIC COLORECTAL MALIGNANCIES

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ABSTRACT

Colorectal cancer (CRC) is an important health problem both globally and in India. It is the third most common malignant tumor and the fourth most common cause of cancer death in the World. In Indian population, there is paucity of literature on efficacy and toxicity profile of conventional vs targeted therapy plus chemotherapy in recurrent and metastatic colorectal malignancies. Present study was prospective study done to evaluate the Response rate and Progression free survival of conventional chemotherapy compared to that of Targeted therapy plus chemotherapy in first line setting in cases of recurrent or metastatic colorectal malignancies and also to assess the toxicity profile and overall survival on these drug combinations. Patients were enrolled from September 2013 to August 2014 and the date of last follow up was 20th June, 2015. Histologically or radiologically proven patients of recurrent and metastatic colorectal malignancies were enrolled for the study. A total of 70 patients were then enrolled into the study arm which received targeted therapy plus chemotherapy. 70 patients of similar demographic profile and disease status were randomly selected who received chemotherapy alone. The median PFS was 4 months and mean PFS was 5.51 months in the chemotherapy arm. The median PFS was 8 months and mean PFS was 7.21 months in the targeted therapy plus chemotherapy arm (p=0.001). The median OS was 19 months and mean OS was 18.03 months in the targeted therapy plus chemotherapy arm (p value <0.001). The overall response rate was 42.85% in chemotherapy arm and 62.85% in targeted therapy plus chemotherapy arm which was statistically significant. The rates of grade III and IV hematological adverse effects was comparable in both arms. There was 27.14% neutropenia, 12.85% thrombocytopenia, 14.28% anemia requiring transfusion and 14.28% cases of febrile neutropenia in chemotherapy arm. There was 30% neutropenia, 10% thrombocytopenia, 17.14% anemia requiring transfusion and 12.85% cases of febrile neutropenia in targeted therapy plus chemotherapy arm. The differences were not statistically significant.

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INTRODUCTION

Colorectal cancer (CRC) is an important health problem both globally and in India. It is the third most common malignant tumor and the fourth most common cause of cancer death in the World (Ferlay *et al.,* 2012). According to Globocan 2012 world data incidence, mortality and 5 year prevalence are 9.7%, 8.5% and 10.9% respectively. CRC is more common in developed nations and there is at least a 25-fold variation in the occurrence of CRC across various regions of the world.

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In India incidence is 6.3%, mortality rate is 7.1% and 5 year prevalence is 4.8%, which is lower than western population (Ferlay *et al.,* 2012). In United States, CRC has the third highest incidence in both sexes with an estimated 1, 42, 820 new cases annually and approximately 50,830 Americans die of CRC (Jemal *et al.,* 2013). Estimated 5-year survival rates also vary widely by region, from 30% in India to 65% in North America. In a report by Yele *et al* the 5-year relative survival was 36.6% for colon and 42.2% for rectal cancer in Mumbai (Yeole *et al.,* 2001). The large differences in incidence are probably due to environmental and geographical factors, which are believed to play a very important role in CRC etiology. In Indian population, there is paucity of literature on efficacy and

toxicity profile of conventional vs targeted therapy plus chemotherapy in recurrent and metastatic colorectal malignancies.

Aim of the study

To evaluate the efficacy of conventional chemotherapy compared to that of Targeted therapy plus chemotherapy in first line setting in cases of recurrent or metastatic colorectal malignancies.

Study objectives

1. To Evaluate the Response rate, Progression free survival and overall survival of conventional chemotherapy compared to that of Targeted therapy plus chemotherapy in first line setting in cases of recurrent or metastatic colorectal malignancies.
2. To assess the toxicity profile of these drug combinations.

MATERIALS AND METHODS

Study design

The current study was planned prospectively to study the safety and efficacy of conventional chemotherapy vs. Targeted therapy plus chemotherapy in recurrent or metastatic colorectal malignancies. Patients were enrolled from September 2013 to August 2014 at Rajiv Gandhi Cancer Institute (RGCI), a tertiary care cancer institute in India and the date of last follow up was 20th June, 2015. Histologically or radiologically proven patients of recurrent and metastatic colorectal malignancies were enrolled for the study.

Patient selection criteria

Inclusion criteria

1. Histologically or radiologically proven cases of recurrent and metastatic colorectal malignancies who have not received any previous chemotherapy.
2. Age between 18-75 years
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, 2
4. Adequate Hepatic and Renal function.

Exclusion criteria

1. Eastern Cooperative Oncology Group (ECOG) PS 3, 4.
2. Coexistent/synchronous malignancies/co morbid conditions
3. Documented Brain Metastases (Brain imaging not required in asymptomatic patients)
4. Pregnant women with colorectal malignancies.
5. The patients who have received adjuvant chemotherapy and the disease free interval was less than 1 year.

Sample size calculation

The reported hospital based annual prevalence of metastatic patients of colorectal cancer at Rajiv Gandhi Cancer Hospital & Research Centre was found to be 44%. The optimum sample size of metastatic patients of colorectal cancer is calculated based on the following formula:

$$n = Z^2_{\alpha/2} \frac{PQ}{L^2}$$

Where P = Prevalence;
Q = 1 – P; L = Permissible error

Further, the sample size is calculated using the above formula assuming that 10% permissible error. Now the required optimum sample size is;

$$n = \frac{(1.96)^2 \times 44 \times 56}{(10)^2} = 94.7 \cong 100$$

Also assuming the 25% lost to follow-up during the sample collection. Therefore, the operational sample size was 125 for the study. As around 30% of these metastatic patients of colorectal cancer go for the targeted therapy with chemotherapy, therefore total sample was divided according to their proportions.

Pre treatment evaluation

Informed and written consent was taken from all the patients. (Thumb impression if the patient is illiterate). Before starting the treatment the Complete Medical History, physical examination and investigations was done as per protocol. Each patient was given chemotherapy in an indoor patient setting.

Chemotherapy regimen

1. **Folfox-4:** Oxaliplatin 85 mg/m2 D1 iv over 90 minutes, Leucovorin 200 mg/m2 iv over 2 hrs, before 5-FU, d1 and 2, 5FU 400 mg/m2 D1, D2 bolus, 5FU 600 mg/m2 D1,D2 iv over 22 hours infusion

   Q x 2 weekly

2. **Folfiri:** Inj Irinotecan 180 mg/m2 D1 iv over 90 minutes, Leucovorin 200 mg/m2 iv over 2 hrs, before 5-FU, d1 and 2, 5FU 400 mg/m2 D1, D2 bolus, 5FU 600 mg/m2 D1,D2 iv over 22 hours infusion

   Q x 2 weekly

3. **Cetuximab+Folfiri, Cetuximab+Folfox:** Inj cetuximab 500mg/m2 along with usual schedule of FOLFOX or FOLFIRI

   Q x 2 weekly

4. **Bevacizumab+Folfox, Bevacizumab +Folfiri:** MG/KG Body weight infusion along with usual schedule of FOLFOX or FOLFIRI

   Q x 2 weekly

Response evaluation

The primary objective of the study was to determine the tumor objective response rate and Progression Free Survival for patients of metastatic colorectal carcinoma as per treatment protocol and had follow-up measurements performed to assess change in tumor size were assessable for response. RECIST response criteria (version 1.1) were used to define the antitumor effects with tumor size defined as the sum of the longest diameter of all target lesions. Responses were assessed

just prior to 7th cycle of chemotherapy and 3 weeks after completion of 12 cycles by clinical tumor measurements and documentation of the tumor size of measurable and non measurable disease, using CT/MRI/PET scans, whatever scan used in baseline evaluation and follow up for individual patient. If the patient showed clinical evidence of progression before 6 cycles or 12 cycles, assessment was done on the same time. All sites with measurable lesions were followed for response. Response based on target and non target lesions was defined as follows:

A complete response required the disappearance of all clinical and radiologic evidence of tumor for at least 4 weeks. A partial response required a > 30% decrease in the sum of the products of the diameters of all measurable lesions or disappearance of one or more non target lesions, also for at least 4 weeks. Stable disease designated a steady-state of disease, which was a response less than a partial response or progression less than progressive disease. In addition, there could be no new lesions or increases in the size of any non measurable lesions for complete or partial remissions or for stable disease. Progressive disease indicated an unequivocal increase of > 20% in the sum of the products of the diameters of all measurable lesions compared with baseline or the appearance of new target or non target lesions. The measurement of time to event variables such as duration of response for responding patients and time to progressive disease were assessed. The progression-free survival was calculated from time of study entry to the first clinical or radiological observation of disease progression.

Toxicity assessment

The National Cancer Institute Common Toxicity Criteria (v. 4.0) were used to grade side effects. Patients had complete blood cell counts evaluation along with KFT & LFTs before the start of each chemotherapy cycle. If patients had an absolute neutrophil count nadir <500/µl (Grade 4 neutropenia), the dose of both chemotherapy agents were reduced by 25% in subsequent cycles. For platelet count nadirs <50,000/µL along with bleeding complications, the dose of both chemotherapeutics in subsequent cycles were reduced by 50%. Dose delays up to 28 days were allowed for patient recovery from study therapy-related side effects. Chemotherapy was discontinued for any life threatening adverse effects like perforation or CNS bleeding or severe cardiac morbidity.

Statistical analysis

The descriptive statistics was done using mean or median and standard deviation or inter quartile range for quantitative variables and categorical variables were presented in frequencies along with respective percentages. The statistical comparisons for quantitative variables were done using Student's '*t*' or Mann-Whitney 'U' test and for categorical variables Chi-square or Fisher's exact test were used as per the nature of data. For survival analysis, log rank test was used for comparison and Kaplan-Meier survival plot was made. All statistical analyses were performed by using SPSS software (Version 21, SPSS Inc, Chicago, IL, USA). The p value less than 0.05 was considered statistically significant.

Observations and results

Patient demographics: Patients were enrolled from September 2013 to August 2014 at Rajiv Gandhi cancer Institute (RGCI), a comprehensive tertiary care cancer institute in India and the date of last follow up was 20th June, 2015. 75 Histological proven chemotherapy naive patients with recurrent or metastatic colorectal carcinoma were screened who were willing to take targeted therapy plus chemotherapy. Of these 75 patients, 2 patients did not meet inclusion or exclusion criteria, 2 withdrew consent, and 1 was not enrolled due to logistics. A total of 70 patients were then enrolled into the study arm which received targeted therapy plus chemotherapy. 70 patients of similar demographic profile and disease status were randomly selected who received chemotherapy alone. Baseline patient and disease characteristics are listed in Table 1. The maximum number of patients was in age group > 50 years with median age 52.5 years (range 18-72) in chemotherapy arm and 53 years (range 22-72) in targeted therapy plus chemotherapy arm. P value for difference in age is not significant (0.741). There were 74.28% vs 72.85% males and 25.71% vs 27.14% females in chemotherapy arm vs targeted therapy plus chemotherapy arm. There were comparable number of patients with PS 0, 1 and 2 in both the subsets as seen in Table 1. The distribution in various age groups is also shown in Table 1which is comparable and not statistically different between the groups. The distribution according to histology is comparable in both arms as shown in Table 1.

Survival and response assessment

The median PFS was 4 months and mean PFS was 5.51 months in the chemotherapy arm. The median PFS was 8 months and mean PFS was 7.21 months in the targeted therapy plus chemotherapy arm. The difference in PFS is statistically significant with p value of 0.001 as shown in Figure 1. The median OS was 14 months and mean OS was 14.38 months in the chemotherapy arm. The median OS was 19 months and mean OS was 18.03 months in the targeted therapy plus chemotherapy arm. The difference in OS is statistically significant with p value of <0.001 as shown in Figure 2.The overall response rate was 42.85% in chemotherapy arm and 62.85% in targeted therapy plus chemotherapy arm which was statistically significant. The disease control rate was 44.28% in chemotherapy arm and 64.28% in targeted therapy plus chemotherapy arm which was statistically significant. There was 1 patient who attained CR in targeted therapy plus chemotherapy arm while no patient achieved CR in chemotherapy arm as shown in Figure 4. The median PFS in the patients who responded to treatment was 8 months vs 3 months in the patients who did not response in chemotherapy arm. The median PFS in the patients who responded to treatment was 10 months vs 3 months in the patients who did not response in targeted therapy plus chemotherapy arm. The median OS in the patients who responded to treatment was 18 months vs 11 months in the patients who did not response in chemotherapy arm. The median OS in the patients who responded to treatment was 21 months vs 14 months in the patients who did not response in targeted therapy plus chemotherapy arm. The rates of grade III and IV hematological adverse effects was comparable in both arms. There was 27.14% neutropenia, 12.85% thrombocytopenia, 14.28% anemia requiring transfusion and 14.28% cases of febrile neutropenia in chemotherapy arm. There was 30% neutropenia, 10% thrombocytopenia, 17.14% anemia requiring transfusion and 12.85% cases of febrile neutropenia in targeted therapy plus chemotherapy arm as shown in Figure 6. The differences are not statistically significant.

Table 1. Baseline Patient and Disease characteristics

Patient characteristics	Chemotherapy arm	Targeted plus chemotherapy arm
Age <50	30(42.85%)	26(37.14%)
>=50	40(57.14%)	44(62.86%)
Sex Male	52(74.28%)	51(72.85%)
Female	18(25.71%)	19(27.14%)
Ecog PS 0	21(30%)	16(22.85%)
PS 1	48(68.57%)	53(75.71%)
PS 2	1(1.43%)	1(1.43%)
Site - Colon	46(65.71%)	41(58.57%)
	Ascending colon-25.71%	Ascending colon-21.42%
	Transverse colon-17.14%	Transverse colon-20.0%
	Descending colon-22.85%	Descending colon-17.14%
Rectum	24(34.28%)	29(41.43%)
Histology-wd adenocarcinoma	7(10%)	6(8.57%)
MD Adenocarcinoma	41(58.57%)	40(57.14%)
PD Adenocarcinoma	22(31.43%)	24(34.28%)
K Ras- Wild	37(52.86%)	40(57.14%)
Mutated	33(47.14%)	30(42.85%)

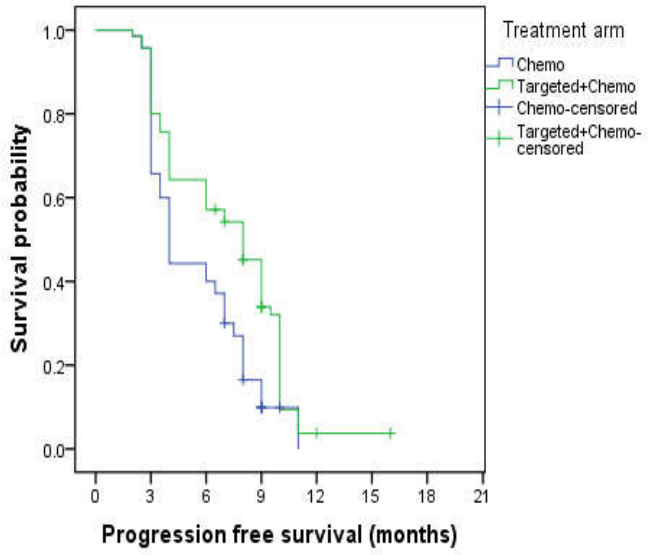


Figure 1. Median PFS comparison between chemotherapy arm and targeted plus chemotherapy arm (KAPLAN MEIER SURVIVAL)

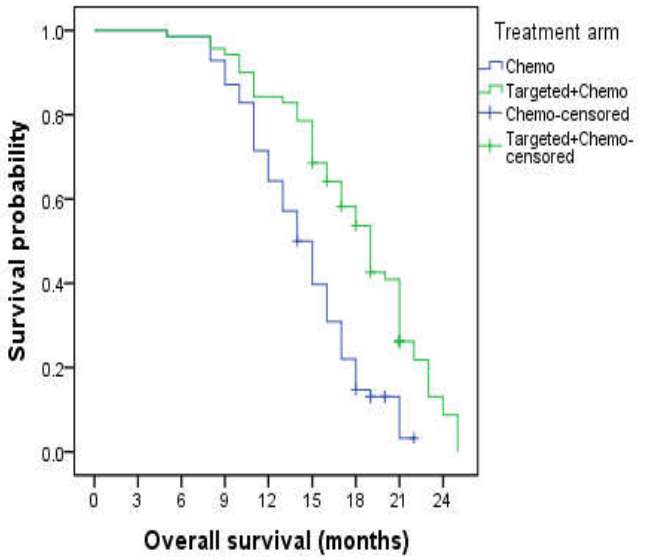


Figure 2. Median OS comparison between chemotherapy arm and targeted plus chemotherapy arm (KAPLAN MEIER SURVIVAL)

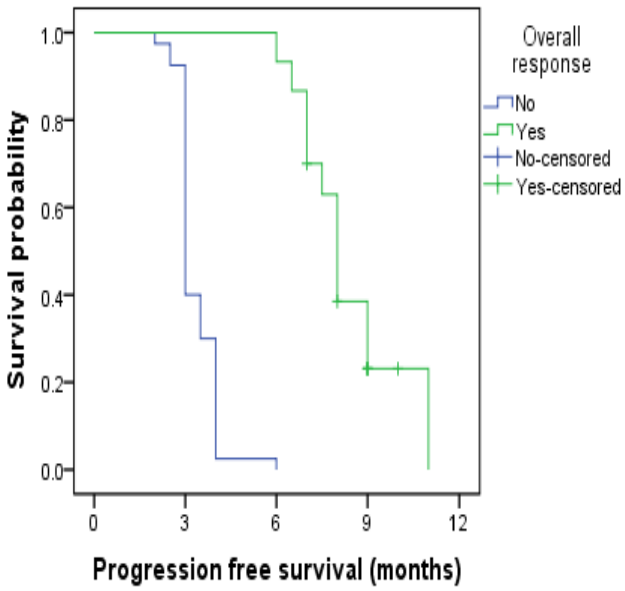
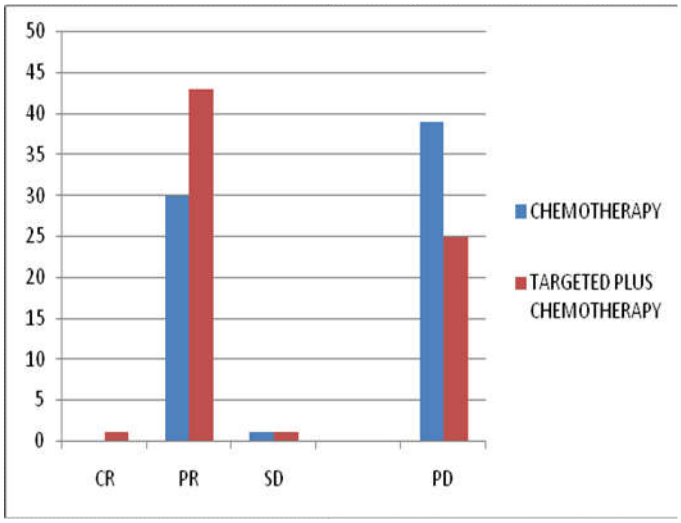


Figure 3. Overall response and kaplan meier survival (PFS) relationship in chemotherapy group



*CR-complete response, PR-partial response, SD- stable disease, PD-progressive disease

Figure 4. Comparison of response between chemotherapy arm and targeted plus chemotherapy arm

Table 2. Comparison of multiple adverse effects and events between chemotherapy arm and targeted plus chemotherapy arm

Event	Chemotherapy ARM	Targeted plus chemotherapy ARM
Diarrhoea grade iii/iv	11(15.71%)	12(17.14%)
Thrombosis	5(7.14%)	9(12.85%)
Bleeding	0	1(1.42%)
Hypersensitivity reaction	2(2.85%)	3(4.28%)
Git perforation	0	0
Hypertension	0	1(1.42%)
Proteinuria	0	2(2.85%)
Cardiac morbidity	6(8.57%)	7(10%)
CNS morbidity	0	1(1.42%)
No of admissions for morbidity	21(30%)	25(35.71%)
Hypomagnesaemia	3(4.28%)	18(25.71%)

*GIT-gastrointestinal tract, CNS- central nervous system

Table 3. Randomised studies with chemotherapy vs targeted therapy plus chemotherapy ARM

Name of study	Arms	Response rate	Pfs (months)	Os (months)
Crystal trial	Folfiri	43.2%	8.7	21
	Cetuximab+folfiri	59.3%	9.9	24.9
Nordic vii [1]	Flox	47%	8.7	20.1
	Cetuximab+flox	46%	7.9	22
Mrc coin[2]	Folfox/xelox	57%	8.6	17.9
	Cetuximab+folfox/xelox	64%	8.6	17
No16966 (Leonard b *et al*)	Folfox/xelox	49%	8	19.9
	Bevacizumab+ folfox/xelox	47%	9.4	21.3
Herbert hurwitz *et al*[16]	IFL	34.8%	6.2	15.6
	Bevacizumab+ifl	44.8%	10.6	20.3
Opus[17]	Folfox	37%	7.2	18.5
	Cetuximab+folfox	61%	7.7	22.8
Prime[18]	Folfox	42%	7.9	20.2
	Panitumumab+folfox	61%	10.1	26.0
Current study	Folfox/folfiri	42.85%	4	14
	Cetuximab/bevacizumab+Folfox/folfiri	62.85%	8	19

Table 4. Randomised studies comparing Ceuximab vs Bevacizumab combination therapies and their comparision to current study

Name of study	Arms	PFS (Months)	OS (Months)
Fire 3[13]	Folfiri+cetuximab	10	28.7
			P=0.017
	Folfiri+bevacizumab	10.3	25
Calgb/	Folfox/folfiri+cetuximab	10.45	29.9
Swog 80405[12]	Folfox/folfiri+bevacizumab	10.84	29.04
Peak [7]	Folfox+panitumumab	13.0	41.3
		P=0.013	P=0.016
	Folfox+bevacizumab	9.5	28.9
Current study	Folfox/folfiri+cetuximab	8	18
	Folfox/folfiri+bevacizumab	8	19

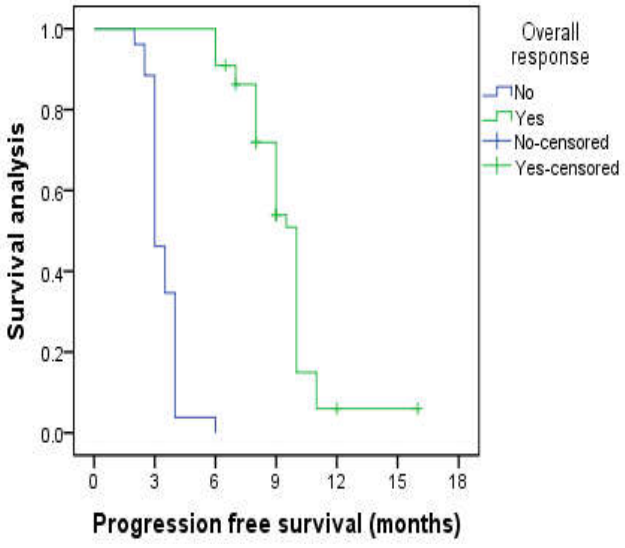


Figure 5. Overall response and kaplan meier survival (PFS) relationship in targeted therapy plus chemotherapy group

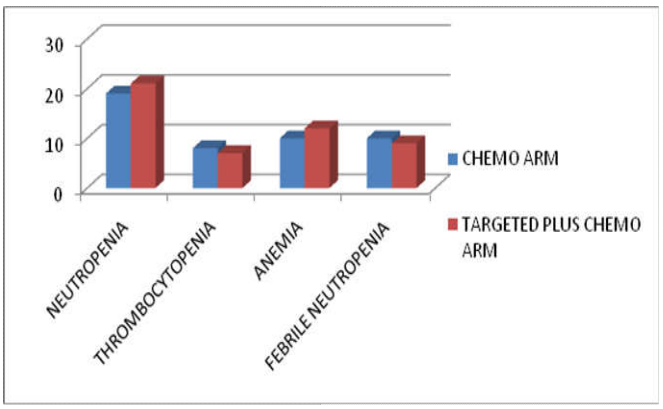


Figure 6. Comparison of hematological adverse effects between chemotherapy arm and targeted plus chemotherapy arm

At the time of data analysis, 10% of patients were alive and 90% dead in chemotherapy arm vs 12.5% alive and 87.5% dead in targeted therapy plus chemotherapy arm.

DISCUSSION

Colorectal cancer (CRC) is an important health problem both globally and in India. It is the third most common malignant tumor and the fourth most common cause of cancer death in the world (Ferlay *et al.,* 2012). The metastatic disease can be either synchronous or metachronous. Approximately 25% of cases have synchronous metastatic disease, while 40-50% cases develop metachronous metastatic disease (Jemal *et al.,* 2013). The treatment of metastatic colorectal carcinoma has evolved from 5FU/LV to addition of irinotecan and oxaliplatin and recently in combination with targeted agents like Cetuximab, Panitumumab, Bevacizumab, Ziv-aflivercept and most recently Ramucirumab and single agent targeted therapy Regorafenib. It has been proved in multiple randomized studies that addition of targeted agents over chemotherapy backbone improves response rate, progression free survival, overall survival and quality of life with acceptable toxicity profile. Indian patients are culturally, geographically and ethnically different from their western counterparts, so the course of disease and response to different chemotherapeutic regimens may be different in an Indian scenario. The present study was prospectively designed to see the efficacy and safety of conventional chemotherapy vs. Targeted therapy plus chemotherapy in recurrent or metastatic colorectal malignancies who presented at a tertiary care cancer hospital of North India. In this study, median age of the patients in the chemotherapy arm was 52.5 years while that in targeted therapy plus chemotherapy arm was 53 years. This age group was very much similar to various randomised studies done with the similar arms. Efficacy wise, it showed significant improvement in all the variables like response rate, progression free survival and overall survival. Tables 3&4 are showing various randomised controlled trials with similar arms and the efficacy parameters.The response rate was 42.85% in chemotherapy arm vs 62.85% in targeted therapy arm, which is comparable to most of the studies. The median progression free survival was 4 months in chemotherapy arm vs 8 months in targeted therapy arm which is showing statistically significant improvement like most of the positive trials of targeted therapy.

The median overall survival was 14 months in chemotherapy arm vs 19 months in targeted therapy arm which is showing statistically significant improvement like most of the positive trials of targeted therapy. There are some negative studies of targeted therapy plus chemotherapy as shown in Table 3. One of the negative studies of Cetuximab was NORDIC VII study, (Tveit *et al.,* 2012) which had various pitfalls like using bolus regime FLOX which had very high toxicity and poor tolerability leading to many dropouts, dose reduction and decrease in dose intensity of the combination. Similarly, in MRC COIN trial (Maughan *et al.,* 2011), again the result was negative for Cetuximab combination chemotherapy, probably because of faulty trial design, dose reductions and dropouts because of adverse effects. The lack of overall survival benefit in these studies was probably because of subsequent treatment received which confounded the overall survival. In the subset analysis, there was no difference between the patients who received Cetuximab based combination vs patients who received Bevacizumab based combination chemotherapy. The median progression free survival was 8 months in both subsets. The response rate was similar with 62.5% in Cetuximab arm vs 63.3% in Bevacizumab arm. The median overall survival was similar with 18 months in Cetuximab arm vs 19 months in Bevacizumab arm. This is being compared to other studies with similar arms in Table 4. In FIRE-3 (Heinemann *et al.,* 2014) and PEAK (Schwartzberg *et al.,* 2014) studies, the Bevacizumab arm was inferior in terms of overall survival. In PEAK study, Bevacizmab arm was inferior in terms of progression free survival as well as shown in Table 4. FIRE-3 trial was criticized for lack of third party review and low rates of second line therapy. The PEAK trial results are different and very encouraging but its criticised for small sample size and limitations of subset analysis. But in the largest randomized study comparing these combinations, CALGB/SWOG 80405 trial (Alan *et al.,* 2014) did not find any difference either in terms of progression free survival or overall survival between the two arms. So either of the combination therapies can be used in patients of metastatic colorectal carcinoma. There is a definite correlation between the severity of skin rashes and the response and efficacy of anti EGFR antibodies (Van Cutsem *et al.,* 2007; Bokemeyer *et al.,* 2009; Douillard *et al.,* 2010). It has been proved in many trials involving Cetuximab and Panitumumab combination. The same correlation was found in current study. In the group of patients who had grade 0 and I rash, the response rate was 30.76%, disease control rate was 30.76%, median PFS was 4 months and median OS was 14 months. In contrast, in the group of patients who had grade II and III rash, the response rate was 77.77%, disease control rate was 81.48%, median PFS was 9 months and median OS was 21 months. This finding was consistent with the previous concept of rash being the surrogate marker of Cetuximab response. Any dose adjustment because of adverse effects was needed in 30% patients in chemotherapy arm vs 34.28 % in targeted therapy plus chemotherapy arm which was not statistically significant.

Similarly any discontinuation because of adverse effects was needed in 11.42% patients in chemotherapy arm vs 14.28 % in targeted therapy plus chemotherapy arm which was not statistically significant. The rates of grade III and IV hematological adverse effects was comparable in both arms. There was 27.14% neutropenia, 12.85% thrombocytopenia, 14.28% anemia requiring transfusion and 14.28% cases of febrile neutropenia in chemotherapy arm. There was 30% neutropenia, 10% thrombocytopenia, 17.14% anemia requiring transfusion and 12.85% cases of febrile neutropenia in targeted therapy plus chemotherapy arm and the differences are not statistically significant.There was 15.71% grade III/IV diarrhoea, 7.14% thrombosis, 2.85% hypersensitivity, 8.57% cardiac morbidity, and 30% rates of admissions for various adverse effects in chemotherapy arm. There was 17.14% grade III/IV diarrhoea, 12.85% thrombosis, 4.28% hypersensitivity, 10% cardiac morbidity like angina, 1.42% bleeding, 1.42% hypertension, 2.85% proteinuria, 1.42% CNS morbidity like cerebrovascular events and 35.71% rates of admissions for various adverse effects in chemotherapy arm. No patient had bleeding, perforation, hypertension, proteinuria or any CNS morbidity in chemotherapy arm. All these adverse effects are very much similar to the multiple randomized studies done. In conclusion, current study reached its primary objective by showing a statistically significant improvement in progression free survival and acceptable and similar toxicity profile to the published literature. It also reached its other end points with significant improvement in overall survival and response rate as compared to chemotherapy arm. There are very few studies regarding outcomes of efficacy and safety of conventional chemotherapy vs. Targeted therapy plus chemotherapy in recurrent or metastatic colorectal malignancies in India. To the

best of our knowledge, there is no published literature of Indian patients regarding the efficacy and safety of conventional chemotherapy vs. Targeted therapy plus chemotherapy in recurrent or metastatic colorectal malignancies. The findings of current study have significant implications for clinical practice. The clinical outcome and toxicity profile of patients receiving Cetuximab or Bevacizumab plus chemotherapy for recurrent and metastatic colorectal carcinoma has been observed to be similar in Indian patients to that reported from the western countries. However, further long term studies and randomized trials on Indian patients are warranted for confirmation.

Conclusion

On the basis of current study at this centre it can be concluded that –

1. Targeted therapy plus chemotherapy is superior to conventional chemotherapy in terms of response rate, disease control rate, progression free survival and overall survival.
2. The adverse effect profile and tolerability are acceptable and similar to published randomized trial studies.
3. There is no difference between Cetuximab and Bevacizumab combinations in efficacy, tolerability and toxicity as per previous randomized studies.
5. To the best of our knowledge, this is the first such study conducted in India. More research and studies are required, especially in the Indian subcontinent, to further assess the efficacy and tolerability of this combination regime in Indian patients. We haven't compared right side vs. left side tumors in terms of RAS mutation and outcome with anti EGFR vs. anti VEGF drugs, which is a drawback of this study.

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