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Research Article

Combination Therapy of Trastuzumab and Lapatinib in Chemorefractory HER2-Positive Metastatic Colorectal Cancer: An Efficacy and Safety Analysis

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Abstract

Background and Objective: In patients with colorectal cancer, some genetic abnormalities are identified in the blood, tumors or metastasis. The prognosis of Human Epidermal Growth Factor Receptor 2 (HER2) in colorectal cancer as a biomarker is uncertain. The use of human epidermal growth factor 2 in treating the receptors targeted with epidermal growth factor has shown a negative response. Hence patients who have HER2-positive colorectal cancer may have very few treatment options and also show poor prognosis. The objectives of the study were to evaluate efficacy and safety with 15 months follow-up of the combination of trastuzumab and lapatinib in patients with HER2+ metastatic colorectal cancer. **Materials and Methods:** A total of 36 patients with HER2+ metastatic colorectal cancer received 4 mg/kg of trastuzumab which is a loading dose and then followed by 2 mg/kg dose once a week and a 1,000 mg/kg dose of oral lapatinib per day until there is evidence of the progressions of the disease (s). Safety parameters evaluated for 15 months follow-up. **Results:** Out of 36 patients, 3 patients (8.3%) had a complete response, 18 patients (50%) had a partial response and 15 patients (41.6%) had shown to have reached an objective response rate. Among 36 enrolled patients, stable disease was found in 9 patients (25%) and 12 patients had disease for more than 3 months (33.34%). Overall, the disease was controlled in 26 patients. The adverse effects of the patients included gastrointestinal, dermatological, nutritional disorders, paronychia, hand-foot syndrome and very few cases of conjunctivitis, an increase in bilirubin in the blood and a decrease in left ventricular ejection fraction. **Conclusion:** The combination of trastuzumab and lapatinib is effective against HER2+ positive metastatic colorectal cancer with manageable adverse effects.

Key words: Trastuzumab, colorectal cancer, HER2 positive, lapatinib, immunohistochemistry

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Colorectal cancer is reported to be the fourth most commonly diagnosed cancer in the world and it is estimated that there are more than 0.1 million new cases of colon cancer and more than 44,000 new cases of rectal cancer alone in 2019¹. It has been found that about 30% of colorectal cancers have genetic etiology and hereditary or familial cases of colorectal cancers account for about 4% of all colorectal cancers^{2,3}. The HER2 or ERBB2 belongs to the tyrosine kinases family and it manages the signaling in the RAS/RAF and PI3K/AKT pathways⁴. Genomic amplification of ERBB2 leads to altered signaling and results in an oncogenic effect, which has been proven in many types of cancers. The application of this kind has been found in adenocarcinoma involving gastric and gastroesophageal junction and also in colorectal cancer⁵. The well-known established target for cancer of the breast and gastric is the Human Epidermal Growth Factor Receptor 2 (HER2). It is known as the oncogenic target. The genomic and functional analysis of the xenografts derived from the patients has proved that mutation or the amplification of the human-derived growth factor receptor 2 causes nearly 5% of metastatic colorectal cancer⁶. In the metastasis of colorectal cancer, ERBB2 amplification occurs in almost 5% of the wild cases⁶. In recent developments, targeting HER2 became the new concept of therapy in several cancers including colorectal cancer. Hence, anti-HER2 drugs are tested in various randomized preclinical trials and encouraging results were obtained including complete responses and the rest of the subjects did not show further evidence of disease with a good median survival^{7,8}.

In patients with colorectal cancer, some genetic abnormalities are identified in the blood, tumors or metastasis. The prognosis of Human Epidermal Growth Factor 2 (HER2) in colorectal cancer as a biomarker is uncertain. The use of human epidermal growth factor 2 in treating the receptors targeted with epidermal growth factor has shown a negative response. Hence patients who have HER2-positive colorectal cancer may have very few treatment options and also show poor prognosis⁹.

Human epidermal growth factors are activated by the process of heterodimerization with the receptors that bind to the ligand. It is done by the mitogenic signals that are created by the heterodimers of HER2 and HER3¹⁰. All the members that belong to the family of epidermal growth factor receptors bind to the ligand except the human epidermal growth factor 2. The overexpression of the HER2 is mainly caused by the amplification of the gene. It helps the activation of the human epidermal growth factor 2 even if there is no ligand¹¹.

The amplification of human EGF-2 (Epidermal Growth Factor 2) in colorectal cancer is explored by using comprehensive genomic sequencing and next-generation sequencing, these are the molecular techniques. The molecular techniques using next-generation sequencing and immunohistochemistry revealed that 1.8% of the patients with human epidermal growth factor 2 positive to colorectal cancer revealed the overexpression of the HER2 and 97% of concordance is seen between gene amplification and protein expression of HER2¹². The studies conducted by Shimada *et al.*¹³ and Schrock *et al.*¹⁴ stated the use of comprehensive genomic sequencing in detecting human epidermal growth factor 2 positive colorectal cancer. They assessed the status of HER2 in 201 patients with colorectal cancer of stages 1-4 using techniques like immunohistochemistry and fluorescent *in situ* hybridization that is compared with comprehensive genomic sequencing, 5% of the patients who are diagnosed with HER2 positive also had amplification of HER2 according to the molecular technique of comprehensive.

The status of the human epidermal growth factor 2 was determined using liquid biopsies from the blood of patients with breast cancer, it was also applied recently to patients with metastatic colorectal cancer¹⁵. The trials conducted on the blockade of the human epidermal growth factor 2 are based on immunohistochemistry. In the future next-generation genomic sequencing may replace immunohistochemistry, though next-generation genomic sequencing is expensive it has an added advantage in capturing a wide range of abnormalities of a genome that includes the mutations that activate the HER2 and also allows the increase in the number of genes copies^{9,16}.

Due to the variation in the embryonic origin the tumors that originate in the left and right side of the rectum and colon show differentiation in epidemiology, mutation and pathology. The proximal tumors differ from distal tumors as the proximal tumors are hypermethylated or they have microsatellite instability. The proximal tumors are more common in the elderly and women. The recent meta-analyses proved that there is a worsening of the tumor on the right side than the left colon¹⁷.

Several studies on colorectal cancer that are based on the pathological and clinical features of the tumor reported a difference in the amplification of the HER2. Based on the analysis of the genetic expression and the DNA copy number, the chemotherapy trial on patients with colorectal cancer revealed that the carcinomas that are distal to the colon are more likely to be an amplification of HER2 than the proximal tumors. In the study about colon cancer based on the PETACC-8 FOLFOX stage 3, no such relation between the

amplification of HER2 and the location of the tumor is found⁹. The prognosis of HER2 in colorectal cancer is uncertain. In the earlier studies, they proved that there is a negative prognosis of HER2 overexpression, but recent studies state that there is no association between HER2 amplification and colorectal cancer¹⁸. Colorectal cancers are the heterogeneous molecular groups of tumors that show mutations in the BRAF, KRAS, PIK3CA and also HER2 amplification. The alterations in the gene showed resistance to the epidermal growth factor receptor-targeted treatment in patients with colorectal cancer¹⁹.

A study that was conducted in the Italian academic cancer center admitted patients with wild-type KRAS exon and HER2-positive metastatic colorectal cancer that is refractory to treatment with cetuximab or panitumumab⁷. Molecular techniques like immunohistochemistry and fluorescent *in situ* hybridization found HER2 positivity in the tumor samples of the patients. The patients who were eligible for the study received trastuzumab and oral lapatinib until there was any evidence of the progression of the disease. The study interpreted that the combination of oral lapatinib and trastuzumab is tolerated and active in patients with HER2-positive metastatic colorectal cancer and refractory to the treatment²⁰. The ERBB2 amplification is seen in 5% of the patients with wild type of metastatic tumors. The analysis of the HERACLES-A trial supports the treatment with the use of trastuzumab and lapatinib for the patients with wild type of metastatic colorectal cancer that is refractory for the treatment with ERBB2 and the wild type of colorectal cancer. The data that is presented by this study also indicates that the central nervous system may present a relapse for colorectal cancer²¹.

Sartore-Bianchi *et al.*⁷ was found that the HER2 inhibition with lapatinib and trastuzumab resulted in the inhibition of the growth of the tumor in the xenografts derived from patients with HER2-positive metastatic colorectal cancer. A study was conducted to assess the activity of lapatinib and trastuzumab in patients who have HER2-positive metastatic colorectal cancer.

In this present study, an investigation has used this drug combination in the clinical trial (HERACLES-A trial) with 15 months follow-up and we determined the effect of this drug combination by assessing the overall survival.

MATERIALS AND METHODS

Study area: The study was performed from March, 2020 to August, 2021 at the Guangzhou Tianhe District People's Hospital, Guangzhou, Guangdong, China and the Children's Hospital of Chongqing Medical University, Chongqing, China.

Ethics approval and consent to participate: The designed protocol of the study was approved by the Human Ethics Committee of the Guangzhou Tianhe District People's Hospital and the Children's Hospital of Chongqing Medical University (Approval number GTDPHgg515175 dated 15 January, 2020). The study follows the law of China and the V2008 Declarations of Helsinki. An informed consent form was signed by all patients before the commencement of the study.

Study population: The HERACLES trial, otherwise called HER2 amplification for colorectal cancer enhanced stratification trial, is used in patients with HER2 positive metastatic colorectal cancer to determine the activity of trastuzumab and lapatinib combination. The HERACLES is a concept of proof, phase 2 trial done at Italian academic cancer centers. Adult patients with wild type of KRAS and metastatic colorectal cancer positive for HER2 were enrolled who are refractory to the treatment with cetuximab or panitumumab. Molecular techniques like immunohistochemistry and fluorescent *in situ* hybridization were used for defining the HER2-positive tumor samples.

Interventions: The patients who are eligible for the study received an intravenous dose of 4 mg/kg of trastuzumab which is a loading dose and then followed by 2 mg/kg dose once a week and a 1,000 mg/kg dose of oral lapatinib per day until there is evidence of the progressions of the disease (s).

Design of the study: This present study consisted of 2 steps. Step 1 is done on a formalin-fixed sample that is embedded in the paraffin. Step 2 was conducted on the wild types of metastatic colorectal cancer patients screened for the HERACLES trial. The samples were processed by the pathology laboratory including those that are already tested for the HERACLES and ERBB2.

Status of ERBB2: The ERBB2 expression was deeply analyzed by the immunohistochemical process that was performed using the Hercep test antibody. This was carried out manually and also by using the VENTANA 4B5 antibody on the automated benchmark ultra system automatically. The VENTANA 4B5 is a monoclonal antibody targeted against an oncoprotein, specifically against an internal domain of c-erbB-2 oncoprotein or HER2 oncoprotein. The amplification of the ERBB2 was done with a DNA probe kit by fluorescence *in situ* hybridization (FISH) and also by using VENTANA 4B5 HER2 which is dual-color on the benchmark ultra system by Silver-enhanced *in situ* hybridization or SISH. The scoring and the evaluation are done by counting the CEN17 and ERBB2

signals for the *in situ* hybridization. Normal mucosa of the colon is used as a negative control. The samples that were presented with a ratio of greater than two in ERBB2/CEN17 are considered amplified.

Analysis: A sample can be presented for the evaluation of review when all the results of the test are present. For the patient to be considered in the study at least one sample should be evaluated. In case there are multiple samples patient is considered to have the highest immunohistochemistry value. In step one, the immunohistochemistry and the *in situ* hybridization scoring procedures are taken into consideration as the standard scoring system in gastric and breast cancers. Only the samples with a ratio of greater than two in the ERBB2/CEN17 or equivocal staining or positive staining are considered in the review. In step 2 only the FISH DNA probe kits and the VENTANA 4B5 are used in determining the ERBB2. The scoring of the samples is given according to the diagnostic criteria of the HERACLES trial. While exploring the use of ERBB2 as a therapeutic agent in colorectal cancer in the trials done by HERACLES, by assessing the dual ERBB2 inhibition activity with the use of lapatinib and trastuzumab an investigation is done on the overexpression of ERBB2 and also its amplification in the metastatic colorectal cancer.

It was established that gastric and breast cancer criteria for the positive determination of the ERBB2 is made suitable to score ERBB2 accurately. The pathologists selected VENTANA 4B5 over the Hercep test for the determination of the protein expression because this test lacks false-negative interpretations and also it helps in recognizing both ERBB2 and ERBB4. In the second one we refined the algorithm of diagnostic ERBB2 which is referred to as HERACLES diagnostic criteria. It focuses on the amplification of the ERBB2 as data in supporting the trial conducted by HERACLES and not only the overexpression as the marker in response to the treatment of anti-ERBB2.

RESULTS

Study population: The authors of this study accepted applications for this trial from 1st March, 2020 to 22nd August, 2021. The study interpreted that the use of lapatinib and trastuzumab in combination is tolerable and functions actively in treating patients who were with HER2-positive metastatic colorectal cancer and were refractory to the standard treatment. In the present study, 36 patients were considered after applying inclusion and exclusion criteria. The patients

were screened with the wild type of metastatic colorectal cancer and 52 patients were identified with HER2-positive metastatic colorectal cancer. Among them, 36 patients were eligible for the clinical trial.

Clinical parameters: The baseline characteristics were shown in Table 1. With the follow-up for about 1 year and 5 months, the data cut-off showed. Median overall survival was 45.2 months/patient which has been found in HERACLES-A trial conducted on the participants. Table 2 for details of this result. This present study found that 3 patients showed complete response (CR) in the follow-up of the study after 15 months. The above survival time is determined right from the start of the therapy targeted against HER2 till the elapsed time since the point when metastatic disease was diagnosed. This is considerable in the HERACLES-A trial. The assessment of the tumor progression and status was done at the baseline and also conducted every 4 weeks till the progression. Since the study has started, a follow-up study has been updated for overall survival (OS). The assessment of the study result was made in terms of the patient's death and also for CNS status. In the follow-up, the patients who returned with CNS features had to go through a Contrast-Enhanced Computed Tomography (CECT) scan using contrast intravenously and hence, they were treated as required in the clinical setting.

These patients were given a combination of trastuzumab and lapatinib. In present study, the age of the patients ranged between 40 and 86 years old. The median age of the patient is 55 years old. Among the 26 patients, there are 28 males and 8 females, accounting for 78 and 23%, respectively.

Table 1: Baseline characteristics of the patients enrolled in the study

Clinical parameter	Value
Numbers of patients	36
Age (years)	55 (40-86)
Gender	
Men	28 (78)
Women	8 (22)
3+	30 (83)
2+	6 (17)
Tumor location	
Colon	27 (75)
Rectum	9 (25)
Distal	20 (56)
Proximal	7 (19)
Prior treatment	
Median number of prior lines	6 (17)
Patients with more than 3 prior lines	28 (78)
Prior treatment with cetuximab or panitumumab	36 (100)

Categorical variables frequencies with percentages in parenthesis, continuous normal variables are depicted as median with Q3-Q1 in parenthesis

Table 2: Overall survival of the enrolled patients

Patient identity	Overall survival (OS) (%)
P001	53.2
P002	47.1
P003	75.5
P004	83.6
P005	33.3
P006	53.9
P007	23.2
P008	39.1
P009	10.9
P010	57.4
P011	29.1
P012	30.6
P013	91.4
P014	62.2
P015	49.1
P016	60.1
P017	24.3
P018	84.7
P019	50.1
P020	47.1
P021	94.9
P022	22.4
P023	45.2
P024	39.9
P025	37.4
P026	30.4
P027	46.5
P028	18.1
P029	29.1
P030	25.6
P031	53.9
P032	19.7
P033	46.3
P034	37.9
P035	43.8
Median value	45.2

Table 3: Number of patients with each adverse effect found in the study

Adverse effects	Grades 1-2	Grade 3
Gastrointestinal		
Diarrhea	25 (69)	2 (6)
Abdominal pain	6 (17)	
Nausea	12 (33)	
Vomiting	7 (19)	
Dermatological		
Rash	19 (53)	1 (3)
Dry skin	11 (31)	
Nail disorder	5 (14)	
Pruritus	6 (17)	
Erythema	1 (3)	
Folliculitis	2 (6)	
Metabolic and nutritional disorders		
Fatigue	13 (36)	1 (3)
Anorexia	1 (3)	
Paronychia	10 (28)	2 (6)
Conjunctivitis	5 (14)	1 (3)
Hand foot disease/syndrome	2 (6)	
Increase in serum bilirubin	2 (6)	
Reduction in left ventricular ejection fraction (LVEF)	1 (3)	1 (3)

Variables are depicted as frequencies with percentages in parenthesis

In this study, the magnitude of HER2 expression was measured by an immunohistochemical process whose score came to be 3+ for 30 patients and 2+ for 6 patients, accounting for 83.34 and 16.67% of the total enrolled patients, respectively. The study found that in 27 patients (75%) colon is the primary site of the tumor which includes 20 patients in the distal colon (55.56%) and 7 patients in the proximal part of the colon (19.4%). Also, 9 patients had shown rectum as the primary site of the tumor which accounted for 25%.

Out of 36 patients, 3 patients (8.3%) had a complete response (CR), 18 patients (50%) had a partial response (PR) and 15 patients (41.6%) were shown to have reached the objective response rate (ORR). Among 36 enrolled patients, stable disease was found in 9 patients (25%) and 12 patients had disease for more than 3 months (33.34%). Overall the disease was controlled in 26 patients.

The adverse effects of the patients included gastrointestinal, dermatological, nutritional disorders, paronychia, hand-foot syndrome and very few cases of conjunctivitis, an increase in bilirubin in the blood and a decrease in left ventricular ejection fraction. Among the 36 patients, 13 patients showed side effects like fatigue, 19 patients had rashes on the skin and 2 patients showed an increase in the concentration of bilirubin. No side effects that are related to the drug are detected in the study. The detailed results of adverse effects were shown in Table 3.

DISCUSSION

Tyrosine kinase activation and over-expression may be initiated from the HER2 amplification in gastric, breast and colorectal cancer. The clinically approved HER2 antagonists include pertuzumab and trastuzumab are monoclonal antibodies, reversible inhibitors like lapatinib which is an ATP mimetic and neratinib and afatinib are irreversible inhibitors²². In the tumors of the mammary gland, trastuzumab is used as an adjuvant that has the potential for surgical treatment. It has been found that the combination therapy of trastuzumab and lapatinib used in HER2-positive cancers to inhibit or reduce the effect of HER2, produces an increase in the survival rate and higher pathological response compared with the use of lapatinib alone²³. The therapeutic effect of trastuzumab in HER2-positive gastric cancer is not satisfactory, although trastuzumab is used in the treatment of gastric cancer as it has produced an advantage when used along with standard chemotherapy. In addition, lapatinib when used in combination with cytotoxics, failed in determining the survival improvement. Hence, the benefits of such combinations had limitations. One of the reasons for these drawbacks is the

selection of patients of fewer criteria and also cases of less heterogeneous copy number of HER2. There is a need to study further with broad criteria and more variants of HER2^{24,25}. The previous evidence suggests that the cancer cell lines of the amplified HER2 gastric cancer indicated that the combination of lapatinib and trastuzumab shows greater antitumor efficiency than when they are used alone. Recent studies demonstrated that in metastatic colorectal cancer that is refractory to the inhibition of Epidermal Growth Factor Receptor (EGFR inhibition), the amplification of HER2 represents a hallmark for them. Preclinical studies stated that monotherapy with anti-HER2 drugs shows poor efficacy in the treatment of tumors^{26,27}.

Only a few patients who have metastatic colorectal cancer can benefit clinically from receiving the therapy of anti-epidermal growth factor receptor (anti-EGFR) antibody. In a study, 85 patients were produced as xenograft cohorts to discover novel targets for oncoproteins and also a therapeutic drug. The tumors maintain the morphological and genomic features of their parent tumor for those that are passed serially. The correlations between genotype and drug response have found that there is an amplification of HER2 in subsets that are resistant to cetuximab, such as wild-type cases like KRAS/BRAF/NRAS/PIK3CA. The amplification of HER2 was enriched in patients with KRAS who are not responsive clinically²⁶. The intensive study on male patients with amplified HER2 proved that the long-lasting inhibition of tumors can be achieved by using human epidermal growth factor receptors and HER2 in combination²⁷. There is an increase in survival of the patients with gastroesophageal carcinoma with the improvements in the treatment being accompanied by the increase in the incidence of brain metastasis that is secondary. In the present study, 20% of the patients with gastroesophageal adenocarcinoma have shown amplification of HER2 that is accompanied by an increase in the metastasis of the brain in patients with breast cancer. Limon *et al.*²⁸ collected data on the clinical features, outcomes of the patients, the status of HER2 and metastasis of the brain in the patients diagnosed with gastroesophageal adenocarcinoma. A total of 404 patients were identified with the confirmed diagnosis of gastroesophageal adenocarcinoma. It was concluded that HER2 results were found in 298 patients among them 69 are positive. Metastasis of the brain is developed in 15 patients. The metastasis of the brain is high in patients with positive HER2 with gastroesophageal adenocarcinoma. A total of 2.3 months is the median survival of the patients with metastasis of the brain. There is no difference in the status of HER2. A lower threshold should be maintained for brain

imaging in patients with positive HER2 gastroesophageal adenocarcinoma as they have an increase in the risk of metastasis of the brain²⁸. Although, there is much research conducted and developments occurred in the management of metastatic colorectal cancer, the survival rate of patients with this disease is still not satisfactory. Activating the HER2 pathway as a bypass signal, it is identified as a mechanism of resistance for the antibody therapy of anti-epidermal growth factor receptors in both the salvage and first-line systems. It is shown that the wild type of metastatic colorectal cancer like the BRAF and RAS has contributed to the presence of the amplification of HER2. The supporting preclinical data has been used to conduct many clinical trials for the dual anti-HER2 targeted therapy. Recent studies suggest that anti-HER2 therapy may provide a significant benefit in treating patients with HER2-positive metastatic colorectal cancer. The studies conducted by HERACLES-A showed benefits in using a combination of trastuzumab and lapatinib in a small number of patients. In our current study, the HERACLES-A trial revealed an objective response rate (ORR) of 29% and a median progression free survival (PFS) of 4.9 months. This result was obtained from the population that was not either pretreated by the standard existing regimens or treated but ORR was significantly low. In this study, work has obtained a complete response (CR) which is significantly sustained for longer times. The result of our study shows that targeting HER2 leads to appreciable clinical benefits and survival rates. In our study, we have found that the median OS (overall survival) is 45.2 (Table 2). More studies are suggested to be conducted before accepting HER2-targeted therapy as a mainstream management protocol. For this, there is a need to collect data continuously from other studies that are being conducted on the management of metastatic colorectal cancer²¹. Alteration in the signaling of human epidermal growth factor receptor 2 is caused by the amplification of the genome of ERBB2 or oncogenic mutations and is seen in multiple cancer types²⁹. The ERBB2 amplification is observed in 15-20% of the patients with breast carcinoma and also in the same proportions in gastroesophageal and gastric carcinomas. This has led to the development of therapeutic antibodies that target this receptor, like pertuzumab and trastuzumab and also lapatinib which is a pan-ERBB molecule inhibitor. Identifying the patients in whom the anti-HER2 is seen to be beneficial, evaluating the amplification of ERBB2 fluorescence *in situ* is performed and to know the overexpression of the protein then immunohistochemistry is conducted, it is part of standard therapy for patients with breast and gastrointestinal tract adenocarcinoma^{5,30}. The recent advances in the ERBB2 amplification and its mutational sequence in patients of

colorectal cancer have found that the drug that should gain importance in this condition is anti-HER2. Moreover, it shows a mechanism of resistance for the epidermal-derived growth factor (EDGF) receptor for targeted treatment therapies such as panitumumab and cetuximab. Again, there are some reports published that concluded that a higher level of ERBB3 amplification may lead to poor prognosis of colorectal cancers, hence, suggesting that HER3 can be considered a new therapy in colorectal cancers^{31,32}. The randomized phase 2 trial (Cher-LOB trial) showed consistent results with previous trials as the *post hoc* survival analysis from the same was conducted for the PCR role in patients who were positive for HER2 and were kept on neoadjuvant chemotherapy along with the anti-human epidermal growth factor 2. By combining the treatment modalities, they showed that PCR is achieved by a high long-term survival rate. Patients who are on PCR showed a 78% decrease in the recurrence survival (RFS) risk at 5 years when compared with invasive disease. This helps in supporting the role of PCR in the patients who are positive for HER2 breast cancer in a single patient as it is already highlighted in the meta-analysis promoted by FDA and also in studies that tested dual blockade of HER2 as neoadjuvant therapy. The positive prognosis that was shown by PCR was observed in the analysis of both ER-negative and ER-positive groups³³. The Cher-LOB trial was not conducted to detect the survival differences along with the treatment but towards the improvement in the survival with lapatinib and trastuzumab given in combination over a single blockade of HER2. In the phase 3 trial of CALGB 40601, there is an improvement of over 68 and 66% in the rates of recurrence free survival (RFS) and overall survival (OS), respectively in seven years. It was reported in combination with trastuzumab and lapatinib than trastuzumab alone. In addition to these findings, other trials like NeoALTTO and NSABP B41 showed an increase in the survival rates with the dual targeting with HER2^{23,34}. Correlative studies were also performed between the microenvironment and biology of the tumor and the survival rates of the tumor. A positive correlation between the baseline levels and the PCR was previously noted in the Cher-LOB trial. The baseline levels of tumour-infiltrating lymphocytes (TIL) are found to be prognostic in the overall study. The findings of the NeoALTTO stated that with each 1% increase in the tumor-infiltrating lymphocytes (TIL), there is a 2.2% decrease in the recurrence-free survival (RFS) risk. The PAM50-based intrinsic subtyping is increasing its clinical relevance in patients who are positive with HER2, but in the present studies, no such correlation has been identified^{35,36}. The platform of neoadjuvant which is endorsed by the FDA in evaluating the interventions has given a cost-effective balance when compared with the adjuvant setting. The sample size

that is required to capture the differences of the PCR is smaller when compared to that required for detecting the survival differences. Although, most of the trials that are conducted for the comparison of the combination of trastuzumab and lapatinib or the trastuzumab monotherapy in the management of HER2-positive patients with breast cancer, they reported an improvement in the rates of PCR with the dual targeting of the HER2 when compared with the single blockade of HER2, many of the trials could not show the survival endpoints.

Overall observations suggest that the improvement in the survival with the dual-target HER2 over the single blockade HER2 reflects a limitation rather than a long-term advantage. Because of this reason although they are of small size the survival rates of the Cher-LOB study gain attention as they provide evidence in the same direction as of the neoadjuvant studies of the dual blockade of HER2^{37,38}.

CONCLUSION

Current study has analyzed the anti-HER2 combination extensively and provided satisfactory evidence to show their efficacy against metastatic colorectal cancer of the KRAS wild variety. This current study has summarised the outcome of this drug combination and also compared it to the outcome when the drugs are used as monotherapy. This study has contributed significantly to finding a new drug combination with its dosage for colorectal cancer which was not studied extensively previously. The mechanism of the drug combination and the disease pathology have been correlated and discussed.

SIGNIFICANCE STATEMENT

This current study has summarised the outcome of trastuzumab and lapatinib combination and also compared it to the outcome when the drugs are used as monotherapy. The study reported that partial response is likely for the combination of trastuzumab and lapatinib with 15 months follow-up for metastatic colorectal cancer of the KRAS wild variety. Anti-HER2 combination of trastuzumab and lapatinib extensively and provided satisfactory evidence to show their efficacy against metastatic colorectal cancer of the KRAS wild variety.

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