Differences Of Carcinoembryonic Antigens Levels Before And After Adjuvant Capecitabine Chemotherapy In Post-Colorectal Cancer Operations In Rsup H. Adam Malik Medan In 2019

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Abstract- Background: The 2006 American Society of Clinical Oncology (ASCO) recommendation states that Carcinoembryonic Antigen (CEA) is checked before surgery to aid in staging or planning of action as well as in assessing the response to adjuvant chemotherapy. Chemotherapy in colorectal cancer can be performed as adjuvant, neoadjuvant, or palliative therapy. One type of chemotherapy in colorectal cancer patients is capecitabine. Capecitabine is a type of adjuvant chemotherapy with oral preparations that has advantages in terms of flexibility of use, is not invasive, and is less costly. Objectives: The purpose of this study was to see differences in CEA levels before and after capecitabine chemotherapy and to determine the effectiveness of capecitabine in postoperative colorectal cancer patients at RSUP H Adam Malik Medan in 2019 Methods: This research is an experimental analytical study, by taking research samples starting from January to December 2019 in colorectal cancer patients who have undergone definitive surgery and underwent chemotherapy for at least 8 cycles. Results: There was a decrease in CEA levels after chemotherapy, namely 4.95 (0.5- 786) ng/ml compared to before chemotherapy, 5.7 (0.5- 876.9) ng/ml with p=0.001. There are complete effectiveness and response from the administration of capecitabine adjuvant chemotherapy after 8 cycles in colorectal cancer patients, namely 17 samples (29.3%). Conclusion: There are differences in CEA levels between before and after chemotherapy with capecitabine in colorectal cancer patients
Keywords: Carcinoembryonic Antigen, colorectal cancer, capecitabine, therapeutic differences

I. INTRODUCTION

According to the American Cancer Society, colorectal cancer is cancer that starts in the colon or rectum. This cancer can also be called colon cancer or rectal cancer, depending on where cancer originated. Colon cancer and rectal cancer are often grouped because they have many features in common. (American Cancer Society, 2017) Early detection at an early stage of the lesion can reduce the morbidity and mortality of this malignancy. Colonoscopy is still a significant detection tool in colorectal cancer. Also, to help diagnosis requires monitoring of non-invasive markers to detect colorectal cancer early. The 2006 American Society of Clinical Oncology (ASCO) recommendation states that Carcinoembryonic Antigen (CEA) is checked before surgery to aid in staging or planning of action as well as in assessing the response to adjuvant chemotherapy. (Wang et al, 2015). From research conducted at RSUP. H. Adam Malik in 2015 - 2017 by Pulungan found that the most detected tumor marker was Carcinoembryonic Antigen (CEA) with 39 cases (95.1%) in colorectal cancer patients (Pulungan, 2019).

The management of colorectal cancer is multidisciplinary. Treatment options and recommendations depend on several factors. Surgical therapy is the main modality for early-stage cancer with curative goals. Chemotherapy in colorectal cancer can be performed as adjuvant, neoadjuvant, or palliative therapy. One type of chemotherapy in colorectal cancer patients is capecitabine (IKABDI, 2014). Capecitabine is a type of adjuvant chemotherapy with oral preparations that has advantages in terms of flexibility of use, is not invasive, and is less costly (Chionh et al., 2017). Patients do not need nursing facilities to provide chemotherapy so that patients feel more comfortable because they can run chemotherapy at home and do not rule out daily activities so that it can improve quality of life. (Fumio, 2002). No study at RSUP H Adam Malik Medan assesses differences in CEA levels as a parameter of the effectiveness and response of capecitabine before and after capecitabine adjuvant chemotherapy in postoperative colorectal cancer patients, so the background for this study. The purpose of this study was to see differences in CEA levels before and after capecitabine chemotherapy and to determine the effectiveness of capecitabine in postoperative colorectal cancer patients at RSUP H Adam Malik Medan in 2019.

II. METHODS

This research was conducted in November 2020 at the General Hospital of the Adam Malik Hajj Center, Medan. This research is an experimental analytical study, by taking research samples starting from January to December 2019 in colorectal cancer patients who have undergone definitive surgery and underwent chemotherapy for at least 8 cycles. This study aims to determine the differences in

CEA levels before and after capecitabine adjuvant chemotherapy in postoperative colorectal cancer patients at RSUP H Adam Malik Medan. In the study, patients were tested for CEA levels before chemotherapy and compared at the time after chemotherapy.

This study was followed by 58 subjects who had met the inclusion criteria. The inclusion criteria of this study were colorectal cancer patients in stage II and III, had definitive surgery, had a histopathological picture of adenocarcinoma, received 8 cycles of capecitabine chemotherapy adjuvant, and had a CEA examination. Meanwhile, the exclusion criteria in this study were patients who had a history of synchronous tumors, patients with a history of other malignancies, and patients with impaired hepatic function. The data obtained were then presented descriptively in the form of narration, proportion distribution table, and statistical analysis of SPSS ver.20. data normality test using the Kolmogorov-Smirnov. If the data is normally distributed, the T dependent test is then performed. If the data are not normally distributed, the Wilcoxon test is performed. The level of significance in this study was $\alpha < 0.05$ with a confidence interval of CI: 95%.

III. RESULTS

This study was followed by 58 subjects who had met the inclusion criteria. The characteristics of research subjects are displayed in the form of the frequency with percentages, mean with standard deviation, and median with minimum and maximum values, and a normality test is performed.

Table 1. Characteristics of Research Subjects

Characteristics	Subject	p-value[a]
Age (Mean, SD)	53,2 ± 13,8	0,280
Gender (n,%)		0,999
Male	29 (50)	
Female	29 (50)	
Clinical Stage		
II	28 (48,2)	0,001
III	30 (51,8)	
CEA levels (ng/ml)		
Before chemotherapy	5,7 (0,5- 876,9)	0,049
After the 8th cycle of chemotherapy	4,95 (0,5- 786)	0,001
Therapeutic response		
Complete	18 (31)	
Partial	12 (20,7)	
Progressive	6 (10,4)	
Stable	22 (37,9)	

[a]Kolmogorov-Smirnov

It is known that the subject characteristics of the 58 research samples meet the inclusion criteria. In this study, the age of the sample is shown as a mean value with a standard deviation of 53.2□13.8 years with p = 0.280. Subjects who were sampled based on gender, respectively 29 samples, p = 0.999. Meanwhile, based on the clinical stage of colorectal cancer subjects, it was found that 28 subjects (48.2%) had stage II colorectal cancer, and 30 subjects (51.8%) had stage III colorectal cancer, p = 0.001. So that statistically, the age and sex characteristics of the sample are normally distributed, while based on the clinical stage, they are not normally distributed. From table 1, it is also found that CEA levels during the study are shown in median values with minimum-maximum values, at the time of initial assessment (before chemotherapy) the mean CEA levels were 5.7 (0.5- 876.9) with p = 0.049. Meanwhile, the CEA value after the 8th cycle was 4.95 (0.5-786) (p = 0.001). Thus, statistically, CEA levels before chemotherapy, and after chemotherapy on the 8th cycle were not normally distributed and not homogeneous (P <0.05).

This table also shows the therapeutic response to chemotherapy using capecitabine. Obtained samples with a complete response, which experienced a decrease in CEA levels> 50% or with a CEA value <3 ng/ml, after undergoing capecitabine chemotherapy as many as 18 samples (31%). Samples that experienced a decrease in CEA levels <30% or with a partial response were 12 samples (20.7%). This study also obtained 6 samples (10%) with a progressive response, where the CEA levels after chemotherapy increased compared to the CEA values before chemotherapy. Meanwhile, 22 samples (37.9%) with a stable response, or there was no change in the CEA value during capecitabine chemotherapy. The differences in CEA levels before chemotherapy using capecitabine and after the 8th cycle of chemotherapy using capecitabine are shown in table 2.

Table 2. Differences in CEA levels before and after chemotherapy

Examination Time	CEA levels (Median, min-max)	p-value[b]
Before chemotherapy	5,7 (0,5- 876,9)	0,001

After chemotherapy	4,95 (0,5- 786)

[b]Wilcoxon test

Based on table 4.2, it was found that there was a clinical difference in the mean CEA level before and after the 8th chemotherapy using capecitabine. CEA levels are shown in median (min-max), the CEA value before chemotherapy, namely 5.7 (0.5-876.9) ng / ml, decreased after chemotherapy using capecitabine, namely 4.95 (0.5- 786) ng / ml. Statistically, the data were nonparametric, so the Wilcoxon test was used and there was a significant difference between the CEA values before and after the capecitabine adjuvant chemotherapy where the p-value = 0.001 (p <0.05). The graph above shows changes in CEA levels before and after chemotherapy using capecitabine. It is known that the mean CEA level before chemotherapy was 59.6 ng/ml, decreased after the 8th cycle, the mean CEA level decreased to 45.6 ng/ml.
The differences in CEA baseline markers against using capecitabine are shown in Table 3.

Table 3. Differences in Baseline CEA Markers Before Chemotherapy

***Marker baseline* CEA**	**Before Kemoterapi**	**p-value[c]**
<5 ng/ml	22 (38%)	0,001
>5 ng/ml	36 (62%)	
Total	58 (100%)	

[c]*Chi-Square* test

Based on table 3, it was found that the clinical baseline CEA markers differed from chemotherapy. Baseline CEA markers were categorized based on chemotherapy group, and obtained before the chemotherapy procedure, 22 samples (38%) had baseline CEA markers <5 ng/ml, and 36 samples (62%) were found with baseline CEA markers> 5 ng / ml. With the Chi-Square analysis, it was found that the p-value was 0.001 which was significant between groups. Whereas the difference in CEA levels at baseline before chemotherapy compared to CEA levels after the 8th cycle of capecitabine chemotherapy and the assessment of the response to capecitabine therapy is shown in Table 4.

Table 4. Differences in CEA levels before and after chemotherapy

	N (%)	**CEA differences (Median)**	**p-value[d]**
Therapeutic response			
Complete	17 (29,3)	-0,6 (1- 90)	
Partial	18 (31)	-3,3 (0,8- 423,3)	0,001
Progressive	7 (12,1)	+11,9 (9- 101,6)	
Stable	16 (27,6)	-0,25 (4- 16,9)	

[D]Kruskal-Wallis test

Because the data were not normally distributed, non-parametric measurements were carried out using the Kruskal-Wallis test. And the data are displayed in median (min-max) results. Table 4.3 shows the differences in CEA levels based on the therapeutic response to capecitabine chemotherapy. There were 17 samples (29.3%) who experienced a complete therapeutic response or experienced a decrease in CEA levels up to <3 ng/ml where the median decrease in CEA levels was 0.6 (1-90) ng/ml.

Meanwhile, 18 (31%) samples that experienced a partial response or experienced a decrease in CEA levels with a median decrease in CEA were 3.3 (0.8-423.3) ng/ml. There were 7 (12.1%) samples with increased CEA levels or progressive levels of 11.9 (9-101.6) ng/ml and patients who did not experience significant changes in CEA levels were 16 (27.6). %) sample. So that statistically, there was a significant difference in the therapeutic response to capecitabine chemotherapy, where p = 0.001.

IV. DISCUSSIONS

Capecitabine can be used for colorectal cancer therapy in several ways, namely as an adjuvant monotherapy therapy, or in combination with other chemotherapy agents for metastases or simultaneously with radiotherapy in rectal cancer therapy (Hirsch, Zafar; 2011). In this study, we used capecitabine as monotherapy for the treatment of colorectal cancer patients who had undergone definitive surgery. Serum CEA is a representative tumor marker for colorectal cancer that is widely used for postoperative surveillance in colorectal cancer patients, as recommended by guidelines issued by the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) (Labianca et al., 2010).

In our study, we found a decrease in CEA levels after undergoing chemotherapy using capecitabine for 8 cycles (5.7 (0.5-876.9) vs 4.95 (0.5- 786) ng/ml (CEA before vs CEA after chemotherapy 8 cycles }). Several studies have also shown a decrease during treatment using capecitabine as monotherapy, where the decrease was between 51-76% (Hoff et al, 2001). In 1993, Ward et al. Suggested that decreased CEA levels were associated with tumor response, while elevated CEA levels indicated disease progression (Ward, 1993). In our study, there was a decrease in CEA levels of ≥ 50% in some samples, indicating a therapeutic response to capecitabine

chemotherapy. Wang et al conducted a study of 136 colorectal cancer patients who experienced metastases, found a decrease of more than 50% in CEA levels after chemotherapy week 4 (Wang et al, 2001). Yu Ping et al, in their study also found that some patients experienced progress before the 8th week of chemotherapy (Yu Ping et al, 2018).

Another study found that in a study the baseline serum CEA levels were measured in all 48 patients before starting chemotherapy. Initially, the CEA increased to 35 (72.9%). All 23 samples in the last group showed elevated levels of CEA. After three cycles of chemotherapy, serum CEA levels were re-measured. CEA levels decreased, maintained, or increased <20% compared to baseline in 33 patients, and increased> 20% in 15 patients (Kim et al, 2018). CEA levels in cancer are known to be associated with preoperative tumor area, tumor outcome prediction, and recurrence. However, regarding the role of CEA in assessing tumor response to chemotherapy, no consensus has been reached, although several investigators have investigated the effectiveness of CEA monitoring for evaluation of tumor response in palliative chemotherapy (Wang et al, 2001). Also, this study showed an increase in CEA levels after chemotherapy. Increased levels of CEA generally reflect disease progression and no one has explained this phenomenon in colorectal cancer patients undergoing chemotherapy (Sorbye & Dahl, 2004). However, because CEA is metabolized by the liver, elevated CEA levels can also result from liver disease. Chemotherapy is often associated with improved liver function, which is also an increase in CEA levels which reflect liver damage (Hermunen, Haglund, Osterlund, 2013).

In this study, it was found that the decrease in CEA results before and after chemotherapy did not exceed 50%. This is in line with the research of Ward et al. first found that decreased CEA was associated with tumor response and increased CEA was associated with disease progression; however, their study included only 33 patients and no trend was seen in changes in patient CEA concentrations at different time points indicated. Wang et al. conducted a study of 136 colorectal cancer patients in which they tested the patients' CEA levels every 4 weeks and defined CEA respondents as colorectal cancer patients with a decrease in CEA of more than 50% after more than 4 weeks. The study demonstrated the usefulness of monitoring CEA in determining response to chemotherapy. While this study also tested its usefulness in determining survival analyzes of respondents and non-responders, it did not examine the use of CEA in monitoring disease progression (Wang, 2015).

De Haas et al. conducted a study on 113 liver metastatic colorectal cancer patients treated with preoperative chemotherapy. They used a threshold value of 20% to determine the respondents for CEA. Their results identified a correlation between the CEA-determined response and the radiologically determined response. In their study, all patients underwent liver resection after a median of seven cycles of chemotherapy with results showing that CEA changes determined by the 20% threshold value could not be used to predict this disease (de Haas, 2010).

The mechanisms behind this surge are poorly understood. It is plausible that certain chemotherapy agents induce increased CEA expression by cancer cells resulting in an initial spike with subsequent decreases in CEA associated with increased tumor killing. This will be supported by preclinical data showing increased CEA production in tumor cell lines in response to drug exposure. Treatment of human colon cancer cell line COLC201 with 5-fluorouracil increased CEA mRNA expression; addition of platinum to 5-fluorouracil increases this expression even further. Chemotherapy can cause cytokine elevations in some patients to trigger an initial CEA spike. This will be supported by preclinical evidence of increased CEA expression in response to interferon- and - and to interleukin-6 (Aquino, 2004).

Early transient increases in CEA (flares) can be seen in patients who received chemotherapy within the first 4-6 weeks of treatment, especially with oxaliplatin. This statement is based on two studies that evaluated the phenomenon of CEA flares and demonstrated that CEA flares (defined as> 20% increase from baseline followed by> 20% decrease from baseline in one or more subsequent CEA tests) may occur in 10% -15% of patients. with chemotherapy-treated metastatic disease. It was reported in this case report with 25 and 87 patients, that CEA flares were associated with a favorable objective response to therapy. The exact mechanism by which different CEA values produce varying results is currently unknown. Better tumor response and survival associated with decreased CEA may be due to reduced tumor burden. However, this does not explain why a normal baseline CEA or CEA flare would have a better therapeutic outcome. Other properties of this antigen may be involved in tumor biology or the pathophysiology of disease progression and metastasis. (Strimpakos, 2010). The limitation of this study is that it is a retrospective study so that the side effects of capecitabine chemotherapy are not fully documented. Then, each sample undergoing chemotherapy is not based on the same week, so that each cycle in each sample can be different.

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