Prognostic Value Of Chemotherapy-Induced Neutropenia In Metastatic Colorectal Cancer At Rsup Dr Sardjito Yogyakarta

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ABSTRACT

Background: Colorectal cancer is the third largest incidence of cancer in the world and is the third most common cause of death in women and men . Five-year overall survival (OS) in colorectal cancer who have undergone metastasis was 10 % . Hematologic toxicity may be a marker of biological activity of cytotoxic drug on various types of cancer . Neutropenia after chemotherapy known to be associated with increased patient survival .
Objective : To establish whether chemotherapy-induced neutropenia is predictive of better outcome in patients with metastatic colorectal cancer (mCRC).
Methods: This research was a case-control study. Subjects were patients with metastatic colorectal cancer in the Cancer Instalation Center Tulip RSUP dr. Sardjito who meet the inclusion and exclusion criteria. Data were analyzed by bivariate analysis using chi square test and multivariate analysis with logistic regression.
Results: Neutropenia present in 26 patients (32.5%) of the total 80 patients of the study. Neutropenia were significantly affect OS (p = 0.001 and OR 7.73, 95% CI: 2.51-23.80). Multivariate logistic regression analysis showed neutropenia and the number of metastases affect OS with p <0.001 and p <0.003.
Conclusion: Neutropenia occurring during the two first lines of chemotherapy for metastases colorectal cancer is associated with better survival. Variables that affect OS is the number of metastases and incidence of neutropenia after chemotherapy.
Keyword : Neutropenia, colorectal cancer, metastases, overall survival

ABSTRAK

***Latar Belakang**: Kanker kolorektal adalah kanker dengan insidensi terbesar ketiga di dunia dan merupakan penyebab kematian terbanyak ketiga pada wanita dan laki-laki. Overall survival lima tahun pada kanker kolorektal yang telah mengalami metastasis adalah sebesar 10%. Toksisitas hematologi dapat menjadi petanda aktivitas biologis terhadap obat sitostatika pada berbagai tipe kanker. Neutropenia pasca kemoterapi diketahui berhubungan dengan peningkatan survival pasien.*
***Tujuan:** Untuk mengetahui apakah neutropenia yang diinduksi kemoterapi dapat menjadi prediktor outcome yang lebih baik pada kanker kolorektal metastasis*
***Metode:** Desain penelitian ini adalah kasus kontrol. Subyek penelitian adalah pasien kanker kolorektal metastasis di poliklinik Tulip RSUP dr. Sardjito Yogyakarta yang memenuhi kriteria inklusi dan eksklusi. Data penelitian diolah dengan analisa bivariat menggunakan Uji chi square dan analisa multivariat dengan uji regresi logistik.*

***Hasil Penelitian**: Neutropenia terdapat pada 26 pasien (32.5%) dari total 80 pasien penelitian. Neutropenia mempengaruhi OS secara bermakna dengan nilai p=0,001 dan OR 7.73 (IK95% 2.51-23.80). Analisis multivariat dengan regresi logistik menunjukkan neutropenia dan jumlah metastasis mempengaruhi OS dengan nilai p<0.001 dan p<0.003.*

***Kesimpulan**: Pasien dengan OS lebih dari 24 bulan dipengaruhi oleh kejadian neutropenia pasca kemoterapi lebih besar 7,73 kali dibandingkan pasien dengan OS kurang dari 24 bulan. Variabel yang mempengaruhi OS adalah jumlah metastasis dan kejadian neutropenia pasca kemoterapi.*

***Kata Kunci** : Neutropenia, kanker kolorektal, metastasis, overall survival*

INTRODUCTION

Colorectal cancer is the third largest incidence of cancer in the world, with 1.4 million new cases diagnosed in 2012. Colorectal cancer is the third most common cause of death in women and men. 54% of cases of colorectal occur in developed countries, with the greatest incidence are in Europe, and the lowest incidence in Africa and Asia[1].

Overal Survivall (OS) colorectal cancer depends on the stage of disease when first diagnosed. Five years OS in colorectal cancer who have undergone metastasis was 10% [2]. OS metastatic colorectal cancer patients who received supportive care only less than 6 month[3]. 5-year survival for colorectal cancer at an advanced stage-regional and terminal decline of up to 70% and 12% [4].

Various studies have reported that hematologic toxicity may be a marker of biological activity of the cytotoxic drug in various types kanker[5]. Another study systematic review and meta-analysis study conducted by Shitara et al[6] in 13 studies of various types of cancer, showed leukopenia known to be associated with increased patient survival.

This study aims to determine whether neutropenia after chemotherapy is prognostic and influence on Overall Survival in metastatic colorectal cancer patients at dr Sardjito Hospital.

MATERIALS AND METHODS

This research uses a case-control study to determine the prognostic value of neutropenia after chemotherapy. The study was conducted at the Integrated Cancer Installation dr Sardjito Hospital in the period January 2012 to December 2015. The research sample in each case and control group are 40 patients, with a total sample of 80 patients. Metastatic colorectal cancer patients (mCRC) receiving chemotherapy in combination with bevacizumab were included in the study. Exclusion criteria were patients who had a history of other chronic diseases and medical records were incomplete

Time recording starts at the beginning of patients diagnosed until the time of taking the data with accompanying patient information was alive or dead. Data management is done using the Statistical Package fo Social Science (SPSS) ver 13.0 To determine the relationship between independent variables with the OS performed bivariate analysis using chi-square test. The results of the bivariate analysis with p> 0,25 will be included in the multivariate analysis using logistic regression with 95% confidence intervals and significance accepted when p <0.05.

To compare the survival in the group with no experience neutropenia and neutropenia after chemotherapy, survival analysis is then performed with a probability of survival was estimated by

the Kaplan-Meier method. Hazard Ratio (HR) and 95% CI were estimated using Cox regression analysis.

This study was approved by ethics committees (Ethical clearance) of human biomedical research ethics committee of the Faculty of Medicine, University of Gadjah Mada, and the permission of the Director of dr. Sardjito. Hospital.

RESULTS

The research data showed research subjects male sex as many as 38 people (47.5%) and female sex amounted to 42 (52.5%). Age of patients with colorectal cancer are in the productive age. Breakdown by age showed subjects who entered the group of young adults (18-40 years) of 8 patients (10%), middle age (41-65 years) of the 37 patients (46.25%), and elderly (> 65 years) by 33 patients (41.25%).

Metastasis to one organ occurred in 64 patients (80%) and multiple metastases occurred in 16 patients (20%). Hearts and lungs are the organs with the highest metastasis of 42 patients (52.5%) and 14 patients (17.5%). There are multiple metastases in 16 patients with lungs and the liver is the organ most frequently occur simultaneously and metastasis was found in 11 patients (13.75%). Type of adenocarcinoma histology type of cancer was found in 77 patients (96.25%) and mucinous adenikarsinoma types found in 3 patients (3.75%).

Neutropenia present in 26 patients (32.5%) and as many as 54 patients (67.5%) patients did not experience neutropenia. In the group with more than 24 months OS neutropenia occurred in 21 patients (26.25%) and neutropenia occurred as many as five patients (6:25%) in the OS in less than 24 months. Grade 2 neutropenia occurred in 22 (27.5%) patients and grade 3 neutropenia found in 4 (5%) patients.

Table 1. Patients Characteristics of Research Subjects with metastatic Colorectal cancer

Variable		N (%)	Mean±SD	Median	*Overall survival*	
					≥24 month	<24 month
Gender	Male	38(47.5)			20	18
	Female	42(52.5)			20	22
Age	<50 years old	25(31.25)	56.63±11	57.5 (28-	12	13
	>50 yearsold	55(68.75)	.13	71)	28	27
Site metastases	Tunggal	64 (80)			38	26
	1. Pulmo	14			10	4
	2. Hepar	42			26	16
	3. bone	3			1	2
	4. VU	5			1	4
	Multiple	16(20)			2	14

	1. lung dan liver 2. Liver and bone	11	1	10
	3. Liver, lung, dan brain	2	1	1
	4. Liver dan VU	1	0	1
		2	0	2
Cancer histology	adenokarsinoma	77(96.25)	39	38
	Adenikarsinoma mucinous	3(3.75)	1	2
Chemotherapy drug	1. Xelox+bev	70(87.5)	36	34
	2. Folfox+bev	6(7.5)	2	4
	3. Folfiri+bev	4(5)	2	2
Neutropenia	Yes	26(32.5)	21	5
	• Grade 2	22(27.5)	20	2
	• Grade 3	4(5)	1	3
	No	54(67.5)	19	35

Bivariat Analysis

The results of the bivariate analysis neutropenia OS variables showed significant difference statistically between the two groups with p <0.001 and OR 7.73 (IK95% 2.51-23.80) with probability neutropenia effect on OS was 89%.

The bivariate analysis variable number of metastases to the OS showed significant difference p< 0.001 and OR 10.23 (IK95% 2.14-48.84) with a probability number of metastases affect overall survival is of 91%.

Table 2. Bivariate analysis of variables of age, sex, neutropenia, number of metastases and cancer histology on Overall Survival by chi-square test

Variable	*Overall survival*				OR	*P*
	≥24 month		<24 month			
	N	%	N	%	(95%CI)	
Age					0.89	
<50years	12	15	13	16.25	(0.34-2.29)	0,809
>50years	28	35	27	33.75		
Jenis kelamin					1.22	
Male	20	25	18	22.5	(0.50-2.94)	0,654
Female	20	25	22	27.5		
Neutropenia					7.73	
Yes	21	26.25	5	6.25	(2.51-23.80)	0.001*
No	19	23.75	35	43.75		
Metastases					10.23	
single	38	47.5	26	32.5	(2.14-48.84)	0,001*
Multiple	2	2.5	14	17.5		

Cancer histology					2.05	
Adenokarsinoma	39	48.75	38	47.5	(0.17-23.58)	0.556
Adenokarsinoma musinous	1	1.25	2	2.5		

* Statistically significant

Multivariate analysis

In the multivariate analysis used logistic regression with enter method, the independent variable has a value of p <25 in the bivariate analysis, the variables neutropenia and number of metastases to the results presented in Table 3.

Tabel 3. Multivariate analysis of variables neutropenia and the number of metastases to the OS with logistic regression test

Variable	*P*	OR	IK95%
Neutropenia	0.001	10.43	2.79-40.04
Metastasis	0.003	15.00	2.459-91.549

Multivariate analysis showed the variables that affect the OS is neutropenia and number of metastases with p <0.001 and p <0.003 .Power of the relationship from the largest to the smallest number of metastases (OR = 15,00) and neutropenia (OR = 10,43).

DISCUSSION

In this study, the mean age of patients was 57 years with an age range 28 years to 71 years. In the study conducted Laurie et al[7] mentions neutropenia and age is proven to affect the outcome of patients, but in the age of the study said influence the outcome of the patients were aged over 75 years.

Neutropenia associated with overall survival significantly, which affects neutropenia independently, with p <0.0017. Mild leukopenia happens after chemotherapy is associated with better survival compared to the condition where no leukopenia or there are severe leukopenia after chemotherapy administration[8]. Neutropenia that occurs due to the use of optimal doses of drugs that affect the patients[9].

Hematological toxicity may reflect the biologic activity of cytotoxic drugs, while the absence of toxicity may indicate the dose of medication that is less, so that the necessary determination per individual dose of the drug that can lower toxicity and improve drugs efficacy[10]. Oxaliplatin known to have a suppressive effect on the bone marrow at specific doses[11]. In this study, there were 76 patients (95%) received chemotherapy oxaliplatin at a dose of 130 mg/m^2, which is based on research Tournigand et al., (2004) dose could trigger myelotoxicity in the amount of 85-135 mg/m^2 intravenously with neutropenia of grade 3 and 4 frequent and the incidence of febrile neutopenia only by 4%. However, only 24 patients (31.5%) experienced neutropenia after chemotherapy. According Delord et al[12], this was due to oxaliplatin plasma clearance is not only based on body surface area only, but will also be affected by factors of age, sex, and serum creatinine. The results of this study

complements several studies conducted in other cancer types that have reached the stage of metastasis. According to Wei et al[5], hematologic toxicity may be a marker of biological activity of drug sitostatica on various types of cancer. In various studies say, neutropenia is a known prognostic factor for patient survival is better in patients with lung cancer, gastric cancer, or ovarian cancer who have undergone metastasis[13], and in breast cancer or esophageal cancer therapy neoajuvan[14].

CONCLUSIONS AND RECOMMENDATIONS

Patients with more than 24 months OS influenced by post-chemotherapy neutropenia incidence of 7.73 times greater than patients with OS less than 24 months with the probability of neutropenia affect OS by 89%. Variables that affect the OS is the number of metastases and neutropenia, with the strength of the relationship of the largest is the number of metastasis (OR = 15.00) and neutropenia (OR = 10.43). The results of this study can be used as one of the new clinical evidence regarding the role of neutropenia in determining the prognosis at the time of initial chemotherapy in patients with mCRC in clinical practice. Cohort studies need to be conducted with a sample of the research with post-chemotherapy neutropenia were more in the group tested, so that research results obtained have a level of evidence better.

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