https://doi.org/10.5272/jimab.2017232.1532

Journal of IMAB
ISSN: 1312-773X
https://www.journal-imab-bg.org

Journal of IMAB - *Annual Proceeding (Scientific Papers).* 2017 Apr-Jun;23(2):

PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH METASTATIC COLORECTAL CANCER TREATED WITH FIRST- LINE CHEMOTHERAPY

Deyan Davidov,
Department of Medical Oncology, Medical University, Pleven, Bulgaria

ABSTRACT

Objective: The aim of this study was to investigate the prognostic significance for survival of certain clinical and pathological factors in patients with advanced or metastatic colorectal carcinoma (CRC) treated with first- line chemotherapy.

Methods: From 2002 to 2011 seventy- four consecutive patients with advanced or metastatic CRC, treated in UMHAT- Dr. G. Stranski, Department of Medical Oncology entered the study. Some patient's characteristics, hematological and pathological parameters, were evaluated for their role as predictors of overall survival. The therapeutic regimens included FOLFOX or FOlFIRI. Survival analysis was evaluated by Kaplan-Meier test. The influence of pretreatment characteristics as prognostic factor for survival was analyzed using multivariate stepwise Cox regression analyses.

Results: In multivariate analysis a significant correlation was exhibited between survival, poor performance status and multiple sites of metastasis. Variables significantly associated with overall survival in univariate analysis were performance status>1, thrombocytosis, anemia and number of metastatic sites >1.

Conclusion: These results indicated that poor performance status, anemia, thrombocytosis as well as multiple site of metastasis could be useful prognostic factors in patients with metastatic CRC.

Keywords: Prognostic factors, Metastatic colorectal carcinoma, Survival,

INTRODUCTION

Colorectal cancer (CRC) is the 3rd most commonly diagnosed and leading cause of cancer death in both sexes in the USA [1]. There have been major advances in the chemotherapy treatment of metastatic CRC in the last 10 - 15 years, involving the introduction of new cytotoxic and molecular targeted therapies. However, use of these newer treatments result in increased toxicities and are prohibitively expensive. Even though TNM staging system has been regarded as a standard staging system for colorectal cancer, there are still variations between patients who have the same stage; a set of patients will have minimal response and rapid disease progression that culminates in death within a year of diagnosis [2]. Many biomarkers have been studied as supplementary tools for further classification of the patients into the subgroups based on the current TNM staging system. It is increasingly recognized that variations within disease course and clinical outcome in colorectal cancer patients are influenced by not only oncological characteristics of the tumor itself but also host response factors [3]. Hence, there is a need for accurate predictors of outcomes from treatment, in particular, in identifying those patients who are more likely to benefit. To understand this heterogeneity, some studies have evaluated molecular markers and clinical prognostic factors to predict treatment response. In a pooled analysis of source data from patients treated with first- line chemotherapy for metastatic CRC in 22 clinical trials, Koehne et al. divided patients into three prognostic groups (low, intermediate, and high risk) according to baseline factors: Eastern Cooperative Oncology Group performance status (ECOG PS), white blood count, alkaline phosphatase (ALP), and number of sites of metastatic disease [4]. The low- risk patients had a median survival of 15 months, intermediate- risk patients had 11 months, and the high- risk patients had 6 months survival. Diaz et al. proved the applicability of Koehne's classification in a limited number of patients treated with irinotecan or oxaliplatin- based first- line chemotherapy [5]. However, little is known about the inûuence of some haematological factors on prognosis. The aim of this study was to explore the prognostic significance for survival of certain clinical and pathological factors in patients with advanced or metastatic CRC treated with first-line chemotherapy.

PATIENTS AND METHODS

A retrospective study was conducted to investigate the possible prognostic factors for survival in metastatic CRC. We reviewed a cohort of 74 patients who had treated with chemotherapy for advanced or metastatic CRC between January 2002 and December 2011 in UMHAT- Dr. G. Stranski, Department of Medical Oncology. Patients had histologically confirmed CRC and were treated initially surgically with tumor resection when possible. All patients had clinical or biopsy evi-

dence of advanced or metastatic disease with at least one measurable lesion. Assessment of extend of disease consisted of chest radiography, abdomen ultrasound and, if necessary, computer tomography of the thorax and abdomen was performed. Treatment schedule consisted of oxaliplatin or irinotecan based chemotherapy regimens. Oxaliplatin- based schedule means intravenous oxaliplatin 80 mg/m^2 on day 1, leucovorin 200 mg/m^2 intravenously on day 1 and 2 and 5- fluorouracil 400 mg/m2 bolus followed by 5- fluorouracil 600 mg/m^2 as continued infusion, with repetition every two weeks. Irinotecan- based treatment means irinotecan 180 mg/m^2 day 1 intravenously, fluorouracil 450 mg/m^2 days 2- 5 intravenously and leucovorin bolus 35 mg/m^2 day 2- 5 intravenously, with repetition every 21 days. Both regimens were applied until disease progression or inappropriate toxicity. Detailed patient characteristics prior to initiation of first- line chemotherapy were acquired from hospital patient records. All patients were consecutive non- selected cases. Patients were not candidates for surgical treatment (either curative or palliative).

Different patient or tumor related factors were entered in the analysis based on characteristics identified by previous studies [6, 7]. Patient- related factors included age (≤60 years or >60 years), gender, World health organization (WHO) performance status, hemoglobin (Hb) level, total leukocyte count, platelet count, alkaline phosphatase (AP), lactate dehydrogenase (LDH). Anemia was defined as Hb <120 g/L in men and <110 g/L in women. Thrombocytosis was defined as a platelet count of > 400x10^9/L. Elevated AP was defined higher than 280 UI/L. Elevated LDH was defined higher than 460 UI/L. Pathologic features was determined from the pathologist's reports. Parameter assessed included site of primary tumor (colon versus rectum), site of metastasis (liver versus others) and number of metastasis (single versus multiple). Follow- up information, including cause of death, was ascertained through a review of clinical notes. Overall survival (OS) calculated as time from start of treatment to death or last contact, was recorded and correlated with the above clinical, hematological and pathological parameters. The OS was estimated by the method of Kaplan and Meier [8]. Variables were studied for influence on survival in a univariate analysis by using the log- rank test, and in a multivariate analysis using the Cox proportional hazard regression analysis [9]. The results were considered statistically significant at the p< 0, 05 levels.

RESULTS

A total of 74 patients with advanced or metastatic inoperable CRC, treated with first –line chemotherapy were analysed regardless of their overall survival. All patients had undergone chemotherapy consisting FOLFOX or FOLFIRI. Baseline demographic and disease characteristics are summarized in Table 1. The median age of patients was 62,7 years (range 39- 76 years) and 48 of patients were > 60 years. The male/ female ratio was 71,6% to 28,4%. The most of the patients were in good WHO- performance status (0-1- 79,7%, 2-3- 20,3%). The most common site of primary tumor was colon- 54 patient (72,9%), the patients with rectum carcinoma were 20 (27,1%). The most common metastatic location was the liver (32,4%) and the lung (22,9%). Most of the patients were with one number of metastatic sites at presentation (81,1%). Hb was found as normal in 51 patients (68,9%) and 23 patients (31,4%) were with anemia. Leukocyte and platelet count were normal in 49 (66,2%) and 56 (75,7%) of patients, respectively. The LDH and AP were elevated in 23 (31,4%) and 19 (25,7%) of patients, respectively. The median follow-up period was 10 months (4- 28 months).

The median OS was 11 months (range 1- 22) months. The following pre- treatment factors were identified as univariate predictors of poor survival (Table 2): number of metastatic sites>1, WHO performance status > 1, elevated platelet counts ≥400x10^9/L, anemia with Hb level <120 g/L in men and <110 g/L in women.

No statistically significant differences were found for the following parameters: age, sex, site of primary tumor, AP level, LDH level, and leukocyte count.

Two factors were found to be significant in multivariate analysis. As shown in Table 3, the major unfavorable prognostic factors were multiple number of metastasis and performance status at presentation >1.

DISCUSSION

Over the last few years there has been an increased interest in clinical and molecular prognostic factors in stage IV mCRC. The reason for this is the recent advances in treatment options which have extended patient survival.

Our analysis included consecutive non- selected patients with advanced or mCRC treated in a single center and all patients were treated outside of clinical trials with palliative chemotherapy. Based on the univariate analysis, we distinguished four prognostic factors that influence survival: worsened PS, thrombocytosis, anemia and multiple site of metastasis.

Various studies on survival factors for advanced or mCRC have resulted in disparate results which probably depict differences in patient population and study design and hence make them difficult to evaluate. Nevertheless, in these studies performance status is established as a fundamental clinical prognostic factor in stage IV CRC [10, 11]. Worsening PS has been definitively associated with advanced disease and poor prognosis and this is confirmed in our analysis. The association between anemia and inferior survival capability has also been demonstrated by Kohne et al. previously in their multivariate analysis of 3,825 patients with mCRC treated with palliative chemotherapy in the setting of

22 multinational trials [4]. Elevated level of platelets is observed as unfavorable prognostic factors in many solid tumors. Recently Baranyai Z. at al. reported thrombocytosis to be valuable predictive factor for poor prognosis in patients with mCRC [12]. Our observations correlated with this report. The number of sites of metastases on presentation is reported to had no influence on overall survival from Assersohn et al. [13] Our findings do not confirm this result.

The main limitations of the present study are inherent to its retrospective nature and the relatively small number of patients. Prognostic factors that can risk stratify patients, predictive biomarkers that can help individualize treatment selection and predict a patient's response to therapy, facilitate the better understanding and treatment of the disease. Despite their adequate prognostic ability, none of the established prognostic models is 100% accurate. In consequence, the search for more accurate markers continues. Novel prognostic factors and more up-to-date models are urgently needed for patients with mCRC, especially in the era of targeted therapies.

CONCLUSIONS

This investigation confirm the potential role of some prognostic factors as survival, poor performance status, multiple sites of metastasis and thrombocytosis as predictive tools in metastatic CRC. Prognostic models should widely be used in the clinical practice to counsel patients, plan surveillance protocols, and select appropriate candidates for inclusion in adjuvant treatment protocols. Further improvements in our ability to predict CRC prognosis will rely on the integration of molecular and genetic markers in the currently established models.

Table 1. Baseline patient's characteristics

Characteristics	Number of patients- 74
Age (years)	39 – 76
39- 60	26 (35,2%)
>60	48 (64,8%)
Gender	
Male	53 (71,6%)
Female	21 (28,4%)
Primary tumor type	
Colon	54 (72,9%)
Rectum	20 (27,1%)
Performance status WHO	
0-1	59 (79,7%)
2-3	15 (20,3%)
Site of metastasis	
Liver	24 (32,4%)
Lung	17 (22,9%)
Others	13 (17,5%)
More than one metastasis	14 (27,2%)
Number of metastatic sites	
1	60 (81,1%)
>1	14 (18,9%)
Hemoglobin level	
Normal	51 (68,9%)
Low	23 (31,1%)
Leukocyte count	
Normal	49 (66,2%)
Elevated	25 (33,8%)
Platelet count	
Normal	56 (75,7%)
Elevated	18 (24,3%)
LDH	
Normal	51 (68,9%)
Elevated	23 (31,1%)
AP	
Normal	55 (74,3%)
Elevated	19 (25,7%)

Table 2. Results of univariate survival analysis.

Factor	Favorable	Unfavorable	HR	95% CI	P- value
Age	<65	≥ 65	1,12	0,48 -1,23	NS
Gender	Female	Male	1,2	0, 76-1,45	NS
Performance status	0-1	2-3	1,36	1,12 -1,88	<0,001
Primary tumor type	Colon	Rectum	1,09	0,86 -1,45	NS
Platelet count	$<400x10^9$/L	$\geq 400x10^9$/L	1,58	1,14 - 2,23	<0,001
AP	Normal	Elevated	1,23	0,96- 1,55	NS
LDH	Normal	Elevated	1,18	0,88-1,47	NS
Leukocyte count	Normal	Elevated	1,38	1,01-1-88	NS
Hemoglobin level	Normal	Anemia	1,78	1,23-2,49	<0,001
Number of metastasis	1	>1	1,37	1,12-2,24	<0,001
Site of metastasis	Liver	Others	1,25	0,91-2,13	NS

HR- Hazard ratio, CI- Confidence interval, NS-Not significant

Table 3. Results of multivariate survival analysis.

Factor	Favorable	Unfavorable	HR	95% CI	P-value
Performance status	Others	2	1,53	1,17 -2,12	< 0,001
Platelet count	< $400x10^9$/L	≥ $400x10^9$/L	1,22	0,89- 1,53	NS
Hemoglobin level	Normal	Anemia	1,31	0,98 -1,69	NS
Number of metastasis	1	Others	1,76	1,22- 2,33	< 0,001

HR- Hazard ratio, CI- Confidence interval, NS- Not significant

REFERENCES:

1. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. *CA: A Cancer J Clin.* 2013 Jan;63(1):11–30. [CrossRef]

2. Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? *Int J Colorectal Dis.* 2012 Oct;27(10): 1347-57. [PubMed] [CrossRef]

3. Li MX, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. *Int J Cancer.* 2014 May 15;134(10): 2403-13. [PubMed] [CrossRef]

4. Kohne CH, Cunningham D, Di Costanzo F, Glimelius B, Blijham G, Aranda E, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol. 2002 Feb;13(2):308-17. [PubMed]

5. Díaz R, Aparicio J, Gironés R, Molina J, Palomar L, Segura A, et al. Analysis of prognostic factors and applicability of Koehne's prognostic groups in patients with metastatic colorectal cancer treated with first- line irinotecan or oxaliplatin- based chemotherapy. *Clin Colorectal Cancer.* 2005 Sep;5(3):197- 202. [PubMed]

6. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton S, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med.* 2000 Jul; 124(7):979-994. [PubMed] [CrossRef]

7. Sorbie H, Koehne CH, Sargent DJ, Glimelius B. Patients characteristics and stratification in medical treatment studies for metastatic colorectal cancer: a proposal for standardization of patient characteristic reporting and stratification. *Ann Oncol.* 2007 Jul; 18(10):1666-1672. [CrossRef]

8. Kaplan EL, Meier P. Non- parametric estimation from incomplete observations. *J Am Stat Assoc.* 1959; 53(282):457- 481. [CrossRef]

9. Peto R, Pike MC, Armitage P, Breslow N, Cox D, Howard S, et al. Design and analysis of randomized clinical trials requiring prolonged observations in each patient II. Analysis and examples. *Br J Cancer.* 1977 Jan; 35(1)1- 39. [PubMed]

10. Kemeny N, Braun DW Jr. Prognostic factors in advanced colorectal carcinoma. Importance of lactic dehydrogenase level, performance status, and white blood cell count. *Am J Med.* 1983 May;74(5);786-794. [PubMed] [CrossRef]

11. Edler L, Heim ME, Quintero C, Brummer T, Queisser W. Prognostic factors of advanced colorectal cancer patients. *Eur J Cancer Clin Oncol.* 1986 Oct;22(10):1231-7. [PubMed]

12. Baranyai Z, Krzystanek M, Jósa V, Dede K, Agoston E, Szasz AM, et al. The comparison of thrombocytosis and platelet-lymphocyte ratio as potential prognostic markers in colorectal cancer. *Thromb Haemost.* 2014 Mar 3;111(3):483-90. [PubMed] [CrossRef]

13. Assersohn L, Norman A, Cunningam D, Benepal T, Ross PJ, Oates J. Influence of metastatic site as an additional predictor for response and outcome in advanced colorectal carcinoma. *Br J Cancer.* 1999 Apr;79 (11-12):1800-5. [PubMed] [CrossRef]

Please cite this article as: Davidov D. Prognostic Factors for Survival in Patients with Metastatic Colorectal Cancer Treated with First- Line Chemotherapy. *J of IMAB.* 2017 Apr-Jun;23(2):1532-1535.
DOI: https://doi.org/10.5272/jimab.2017232.1532

Received: 08/01/2017; Published online: 04/05/2017

Address for correspondence:
Deyan Davidov,
Department of Medical Oncology, Medical University,
1, Kliment Ochridski Boul., 5800 Pleven, Bulgaria.
E-mail: dean_davidov@abv.bg