OPEN ACCESS Freely available online

Advances in Medical Research

Research Article

Prognostic value of Interleukin-8 in Colorectal Cancer

Jihene Ayari1,3, Najet Mahjoub2,3, Mehdi Balti1,3, Rania Fehri2,3, Abderrazek Haddaoui1,3

1Medical Oncology Department, Main Military Hospital, Tunis, Tunisia

2Medical Oncology Department, Regional Hospital of Jendouba, Tunisia

3Faculty of Medicine, University of Tunis El Manar, Tunis, Tunisia

ABSTRACT

Background

Colorectal cancer is the third most common malignancy and 4th most common cause of cancer mortality worldwide. Pro-inflammatory cytokines may promote tumor malignant progression, invasion, and metastasis.

The aim of this study was to measure serum levels of circulating IL8 and their correlation with conventional clinic-pathologic prognostic indicators in colorectal cancer in Tunisia.

Methods

Serum samples were prospectively collected from a cohort of sixty colorectal cancer patients. Circulating levels of IL8 were measured with the technique of a solid-phase, two-site chemo-luminescent enzyme immune-metric assay (Immulite 1000, Simens, USA).

Results

The mean age of patients were 58 years (24 – 82 years), 36 men and 24 women with sex ratio:1.5. According to TNM stage we have found: 23.1% stage I and II, 35 % stage III and 41.7% stage IV, 25 patients were metastatic (60% in liver). Ras test was held on 20 Patients in which 13 were mutated one. Pre-treatment serum levels of CEA and carbohydrate antigen 19-9 were elevated on 26.6 % patients and 16.7% respectively. Among patients who had curative therapy (41 patients), only eleven relapsed with a median delay of 4.5 months. The mean level of IL8 was 61.9 þ/- 159.71pg/ml (min 5, max 1173pg/ml). We have found a significant correlation between high level of IL8 and advanced disease (p =0.001) especially with metastatic one (p =0.002) mutant RAS (p= 0.001), patients who had elevated pre-treatment CEA and CA19/9 levels and recurrent disease (0.032).

Conclusion

Our results highlight the role of IL8(CXCL8) in the serum as potential prognostic biomarkers in colorectal cancer patients which could contribute to tumor growth and progression. It could be a potential indicator for detecting colorectal cancer, predicting prognosis and an important target therapeutic in the future.

Keywords: Diagnosis, Prognosis, Colorectal neoplasms.

INTRODUCTION

Colorectal cancer "CRC" is one of the most common cancers worldwide with 1.8 million newly diagnosed cases in 2018 and an important source of cancer-related death with 881,000 cases of deaths [1]. In Tunisia, the incidence of CCR is estimated at 5.4 cases/100000/year in men and 4.8/100000/year in women between 1999 and 2003 [2].

***Corresponding Author:** Jihene Ayari, Medical Oncology Department, Main Military Hospital, Tunis, Tunisia; Tel: 0021627393789, Email: jihen.braham@yahoo.fr

Received date: November 22, 2020; **Accepted date:** August 28, 2021; **Published date:** September 9, 2021

Citation: Jihene A (2021) Prognostic value of Interleukin-8 in Colorectal Cancer. Adv Med Res.Vol.4 .p144.

Extrinsic factors such as environmental, sedentary lifestyle, obesity, smoking, alcohol use play an important role in its development [3] and intrinsic factors such as genetic and chronic inflammatory bowel disease are associated with an increased risk of colorectal cancer [4].

Recent evidence has expanded the concept that inflammation is an essential component of tumour progression. In fact, The relationship between chronic inflammatory diseases and the CCR is a notable example of the close link between inflammation and cancer [5]. It is now becoming clear that the tumor microenvironment, largely orchestrated by inflammatory cells, is an indispensable element involved in the carcinogenesis process, promoting proliferation, survival and migration. Tumour cells secrete cytokines, chemokines and their receptors that promote invasion, migration and metastasis [6].

The aim of this study was to measure serum levels of circulating IL8 and their correlation with conventional clinic-pathologic prognostic indicators in colorectal cancer in Tunisia.

MATERIALS AND METHODS

This was a prospective study involving 60 patients with CRC who under-signed a pre-approved consent by the ethics committee of the Tunis Main Military Training Hospital (HMPIT). Our study was conducted over a period of nine months; from February 2018 to October 2018. Clinico-pathological parameters were identified from clinical records. Patients who were excluded from our study are those with incomplete records, patients who died before February 2018, diagnosis of colorectal cancer that was not confirmed as a primary tumor, and nonTunisian origins.

In our study the serum assay of IL8 was performed by the chemiluminescent solid-phase immunometric assay by the automate IMMULITE 1000 (Siemens, USA)(Appendix 1).

Serum IL8 values were expressed in pg/ml with a reference value of 62 pg/ml.

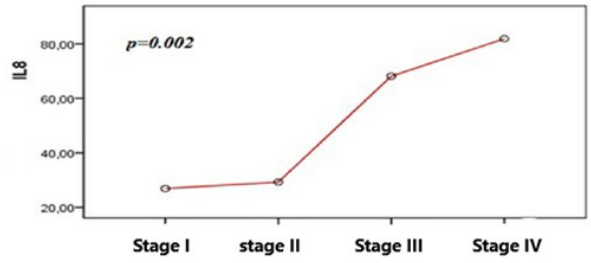
The descriptive and analytical statistical study was conducted using the Statistical Package for Social Science (SPSS) software version 22.0. The results were expressed in number of cases and percentage for qualitative variables and in mean and standard deviation for quantitative variables.

The value of p = 0.05 was fixed as a threshold value below which a difference is taken as statistically significant.

RESULTS

The average age of patients was 58 years (24 - 82 years). The sex ratio was 1.5 with male predominance. Forty patients had at least one personal risk factor of which 3.3% were alcoholic, 26.7% were smoking and 36.7% had other factors such as hypertension and diabetes.

Figure 1: Kinetics of the circulating IL8 curve in pg/ml according to the tumor stage.



The most frequently observed stage was Stage IV (41.7%), followed by Stage III (35%), Stage II (21.6%) and Stage I (1.7%). Metastasis were hepatic in 60% of cases and extra-hepatic in 40% of cases (Table 1). The RAS status was performed in 20 patients, of which thirteen had mutated RAS status and seven wild one (Table 1).

Figure 2: Circulating IL8 levels in pg/ml according to tumor stage.

M: metastatic disease.

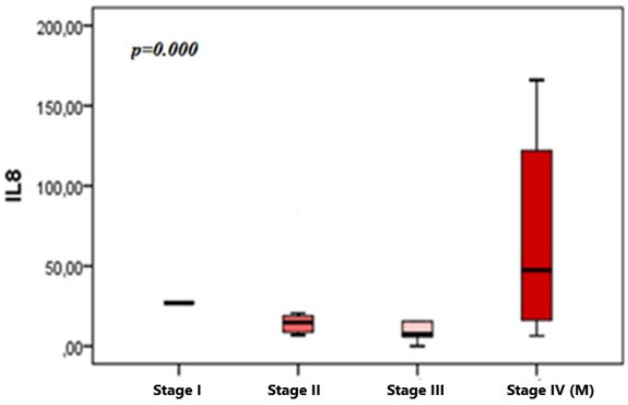


Figure 3: Circulating IL8 level in pg/ml according to RAS status.

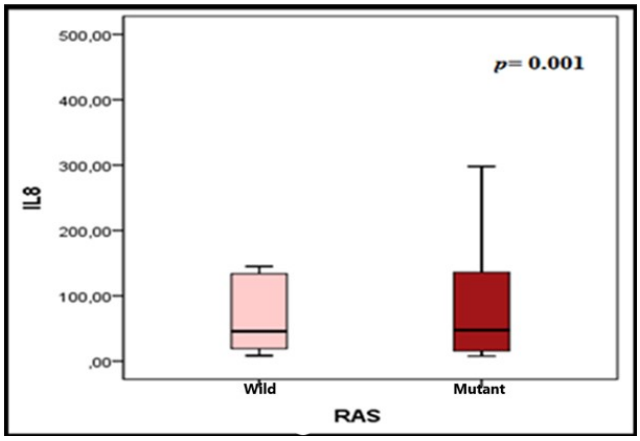
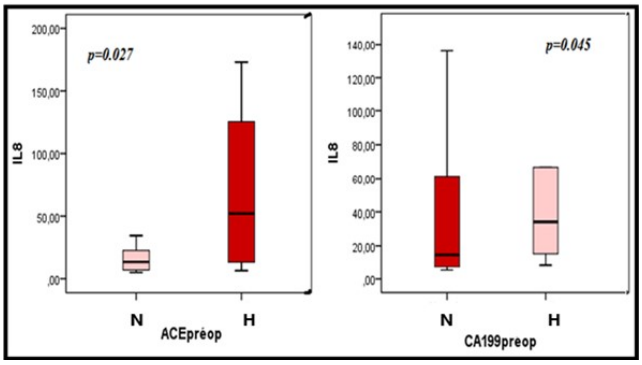


Figure 4 : Association between serum IL8 level in pg / ml and Pre-operative tumor markers ACE, CA19 / 9 (N: normal level, H: High level).



Among the 60 patients with CRC, 18 patients had vascular emboli with 30% of cases and 13 patients had peri-nervous clutch with 21.7% of cases. In preoperative, tumour marker assay showed high ACE levels in 26.6% of cases and 16.7% of cases for CA19-9. Among the 41 patients who had curative treatment eleven had relapsed with a median delay of 4.5 months.

Table 1: Association between serum IL8 level in pg / ml and clinico- pathological factors.

Mean of Circulating IL8 level in pgml +/- ecart type	
Sex, nb women :24	42.70+/- 71.73
Men :16	74.71+/- 197.98 p=0.28
Age, nb < 45 years :13	132.4+/- 347
> 45 years :47	31.67 +/- 45.27 p=0.885
Stage, nb stage I and II : 14	29.28+/- 43
Stage III : 21	68.16+/-247.46 p=0.002
Stage IV : 25	81.89+/- 90.5
Metastatsis,nb M+: 25	116.95+/- 236.2
M-: 35	22.59+/- 32.62 p=0.000
Ras status, nb wild type: 07	96.78+:- 111.34
Mutant: 13	162.45+/- 315 p=0.001
NR:40	23.13+/- 31.76
ACE, nb, Normal : 22	74.84 +/- 246.8
High :16	77.87 +/- 85.8 p=0.027
NR : 22	37.37 +/- 6.71
CA19/9, nb Normal: 28	72.29 +/- 219.66
High: 10	77.83+/- 98.9 p=0.045
NR: 22	37.37 +/- 67.1
Relapsed disease or progression,	147.66+/- 343.9
Yes: 11	26.1 +/- 38.34 p=0.0332
No: 24	

p: signification; n: number of patients; M+: metastatic disease; M-:Non metastatic disease; NR: Not realized

The mean level of serum IL8 was 61.9 +/- 159.71pg/ml (min 5, max 1173pg/ml (Table I). In our study we found a significant association between high level of circulating IL8 and advanced disease (p =0.001) especially with metastatic one (p =0.002) (figure 1, 2); mutant RAS p= 0.001 (figure 3), patients who had elevated pre-operative CEA and CA19/9 levels (figure 4) and relapsed or progression disease p=0.032 (Table I).

DISCUSSION

Cancer is one of the major causes of mortality and morbidity worldwide, accounting for 9.6 million deaths in 2018 [1].

Colorectal cancer ranks second in terms of mortality with 881,000 people having lost their lives this year (9.2%) after lung cancer (18.4%) [1].

In Tunisia, the incidence of CRC is estimated at 5.4 cases/ 100000/year in men and 4.8/100000/year in women [2]; According to the 2014th World Health Organisation(WHO) , CRC occurs in 631 cases/year in men and 572 cases/year in women in Tunisia [7].

Recently, it has been shown a relationship between inflammation, angiogenesis and tumor progression.

The objective of our study was to assess the diagnostic and prognostic value of circulating IL8 (a pro-inflammatory cytokine) in the CRC.

several studies have shown that inflammation and cancer use similar developmental mechanisms, such as cell proliferation and angiogenesis. The prolonged presence of inflammatory cells and its mediators (Cytokines of inflammation) in the tumour microenvironment has been shown to accelerate growth and inhibit apoptosis of transformed cells [8]. Through this study we tried to study the serum profile of a pro-inflammatory cytokine IL8 and assess its diagnostic and prognostic value in colorectal cancer by studying its association with clinical and histological prognostic factors.

Interleukin 8 (IL-8, CXCL8) is a pro-inflammatory chemokine. It is part of the Cysteine X Cysteine family chemokines. IL8 is composed of 99 amino acids and produced by various types of immunity cells. IL8 has two G-protein-coupled receptors: CXCR1(IL8RA) and CXCR2(IL8RB). IL8 has a high affinity for both receptors [9].The acquisition of IL-8 and/or its CXCR1 and CXCR2 receptors is a relatively common phenomenon during tumour progression. Indeed, several studies have shown that IL-8 and its CXCR2 receptor are two of the most positively regulated chemokines in colorectal cancer [10].

The IL8 binding to its receptor causes its biological action by several signaling pathways: Akt, mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT)-3, extracellular signal-regulated kinase (ERK)1/2 and SNAIL promoting the proliferation, angiogenesis, migration of tumour cells and tumor progression through epithelial-mesenchymal transition (EMT). IL8 which acts as an autocrine and a paracrine growth factor, impairs tumor microenvironment via Tumor-associated macrophages (TAMs), neutrophils, cancer

cells, Treg cells, endothelial cells (ECs), mesenchymal stem cells (MSCs), cancer-associated fibroblasts (CAFs) [11].

IL8 may have a diagnostic value in colorectal cancer detection and it may represent a helpful biomarker for identifying high-risk patients although its diagnostic accuracy is moderate [9].In fact in our study, we observed that the serum IL8 level was significantly high with high ACE rate (p= 0.027) and high CA19-9 rate (p= 0.045) respectively.

A meta-analysis including a total of 18 eligible studies on the impact of IL-8 expression on the prognosis of colorectal cancer and its clinico-pathological characteristics suggested that overexpression of IL-8 is significantly associated with poor prognosis in colorectal cancer [12]. Several literature data showed a positive correlation between IL8 serum level, its tissue concentration and CRC stage [12]. Li and al cultured two colorectal cancers cells derived from mice with high and low level of IL8. They observed a different metastatic evolution between both. This shows that there is a significant correlation between IL8 and invasion [13].

CXCL8 and its receptors (CXCL8-R) are involved in almost the entire progression and metastasis process in colorectal cancer [14]. CXCL8 and CXCL8-R promote the proliferation, invasion, migration and angiogenesis of cancer cells and induce the epithelial-mesenchymal transition (EMT) phenomenon of cancer cells, which contributes to the adhesion and intravasation of tumour cells in the blood to become circulating tumour cells (CTC). Most of these cells will be killed by the immune effector cells. However, a small number of them can escape immuno-surveillance and survive in the blood due to the secretion of IL8 which promotes immune resistance and autophagy. Because of the blood flow and CXCL8 axis chemotaxia, CTC can travel long distances, inducing distant locations including the liver [14].

These data were also found in our study. Indeed, we observed that the serum IL8 rate was significantly high with advanced stages (p= 0.002), metastatic one (p=0.000), K-RAS mutated status (p=0.001), and the occurrence of relapse (p=0.032).

Thus we can conclud that circulating IL-8 can be considered a bio-marker of poor prognosis. And Targeting the CXCL8/CXCL8-R signaling axes can be a potential new therapeutic strategy to control cancer progression and overcome drug resistance in colorectal cancer.

CONCLUSIONS

Colorectal cancer is a real public health problem. Recent data have confirmed that inflammation is an essential component in the process of carcinogenesis in CRC. Circulating IL8 could be considered a potential prognostic biomarker in colorectal cancer by identifying patients with poor prognosis requiring aggressive treatment and patients at high risk for recurrence requiring closer monitoring. Targeting the CXCL8/CXCL8-R signaling axes may be a potential new therapeutic strategy to control cancer progression and overcome drug resistance in colorectal cancer.

Nevertheless, we are aware that this work requires further clinical studies with a larger workforce and over a longer period to better understand the inflammatory profile and its correlation with the CCR and the particularity of Tunisian patients and to validate the diagnostic and prognostic value of this bio- marker. Further studies of molecular biology would be possible to determine the secretory origin of these cytokines; the immune cells or tumor cells.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Ahmedin J, et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Can J Clin. 2018;68:394-424.
2. Haggar FA ET, Boushey RP. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. Clin Colon Rectal Surg. 2009;22(4):191-197.
3. Williet N, Anthony LA, Peyrin BL. Maladies inflammatoires chroniques de l'intestin et cancer colorectal: quel est vraiment le risque à l'ère des biothérapies? Hépato-Gastro Onco Dig. 2013;20:325-334.
4. Klampfer L, Cytokines, Inflammation and Colon Cancer.Curr Can Drug Targ. 2011;11(4):451-464.
5. Coussens LM, ET Werb Z. Inflammation and cancer. Nat Pub Gr. 2002;420:860-867.
6. Ayari jihene, Guesmi Rania. Inflammation et cancer du colon. ISBN :6139521645. EUE. 2019.
7. Korniluk A, Koper O, Kemona H, Dymicka-Piekarska V. From inflammation to cancer. J Med Sci. 2017;186:57.
8. Wen-Jun Jin, Jin-Ming Xu, Wen-Li Xu, Dong-Hua Gu, Pei-Wei Li. Diagnostic value of interleukin-8 in colorectal cancer: A case-control study and meta-analysis. World J Gastroenterol. 2014;20(43):16334-16342
9. David JM, Dominguez C, Hamilton DH, Palena C. The IL-8/IL-8R Axis: A Double Agent in Tumor Immune Resistance. Vac J. 2016;4(3):22.
10. Xia W, Chen W, Zhang Z, Wu D, Wu P, Chen Z, et al. Prognostic Value, Clinicopathologic Features and Diagnostic Accuracy of Interleukin-8 in Colorectal Cancer: A MetaAnalysis. PLOS ONE. 2015;10(4):123484.
11. A. Li, M.L. Varney, R.K. Singh, Expression of interleukin 8 and its receptors in human colon carcinoma cells with different metastatic potentials, Clinical cancer research: an official journal of the American Association for Cancer Research. 2001;7(10):3298-304.
12. Yan Ning, Heinz JL. Targeting IL-8 in colorectal cancer.Expert OpinTher Targets. 2012;16(5).
13. HSAIRI M, Hizem Ben Ayoub W, Ben Khadra H, Khiari H. Registre des cancers NORD-Tunisie: données 2007-2009. Tunis: Funziusinesgraphiques. 2017.