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Research Article

Prognostic Value of Pro and Anti-inflammatory Cytokines in Colorectal Cancer

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Abstract

Background: Colorectal cancer is the fourth most common cause of cancer mortality worldwide. Pathophysiology implicates pro-inflammatory conditions that promote tumor progression. The aim of this study is to measure level of cytokines: interleukin (IL) 1β, IL6, IL8, IL10, IL22, IL23 and TNFα and evaluate their prognostic implication.

Methods: Serum samples were collected prospectively from a cohort of sixty colorectal cancer patients in Tunisia. Levels of TNF-α, IL1β, IL6 and IL8 were measured using the technique of a solid-phase, two-site chemo-luminescent enzyme immune-metric assay. Serum levels of IL10 were measured by enzyme-linked immunosorbent assays (ELISA) sandwich method.

Results: The mean age of patients is 58 years (24–82 years), with sex ratio of 1.5. Twenty-five patients were metastatic, with hepatic metastasis in 25% of cases. The mean level of IL6, IL10, TNFα, IL8 and IL1β were respectively 12.29 +/- 18.7pg/ ml, 0.93 +/- 5.23 pg/ ml, 8.31 +/- 4.99 pg/ ml, 61.9 +/- 159.71pg/ml and 1.13 +/- 3.34 pg/ ml. We found a significant correlation between a high level of IL8 and metastatic disease (p=0.000), especially in mutant RAS cases (p=0.001). We also found a significant correlation between high level of IL1β and lymphovascular invasion (p=0.013) and young patients (p=0.01). On the other hand, there was significant correlation between IL8 and IL6 (p=0.00001); IL8 and TNFα (p=0.001); and IL10 with IL1β (p=0.021).

Conclusions: Our results highlight the role of circulating IL8, TNFα, IL1β and IL10 as potential prognostic biomarkers in colorectal cancer patients, namely for IL-8.

Keywords: Inflammation, Cytokines, Interleukins, Colorectal cancer

Introduction

Colorectal cancer (CRC) is the first digestive cancers and is considered to be a major public health issue. In the world, the CRC ranks the third place in terms of incidence with 1.8 million of new cases in 2018 (10.2%) and second place in terms of mortality with 881,000 cases of death (9.2%) [1]. In Tunisia, the incidence of CRC is estimated at 14.2 cases/100,000 in men and 12.1 cases/100,000 in women. Several risk factors such as age, hereditary factors, lifestyle and chronic inflammatory bowel disease can play an important role in its development [2,3]. Inflammation plays an important role in carcinogenesis. In fact, the relationship between chronic inflammatory disease and CRC presents a notable example of the strong relation between inflammation and cancer [4].

The tumor microenvironment, dominated by inflammatory cells, is an essential element participating in the neoplastic process thanks to cytokines, promoting proliferation, survival and migration. In addition, tumor cells recruit some of the cytokines, chemokines and their receptors for invasion, migration and metastasis [5]. Cytokines are innate immune system signaling molecules produced by various types of cells, such as structural, inflammatory, and tumor cells, which allow communication between cells.

In this context, it seemed relevant to assess the profile of pro and anti-inflammatory cytokines, in particular TNFα, interleukins (IL): IL1β, IL6, IL8, IL10, IL22 and IL23 in a cohort of sixty patients followed for CRC at the Tunis Main Military Hospital (HMPIT), and to study the implication of these biomarkers in the prognosis of CRC.

Methods

This is a prospective study including 60 patients with CRC who have signed a consent pre-granted by the ethics committee of the Main Military Hospital of Tunis (HMPIT). Our study was conducted over a period of nine months; from February 2018 to October 2018. The clinico-pathological parameters were recorded from the clinical files. The patients who were excluded from our study are those with incomplete records, patients who died before February 2018, diagnosed with colorectal cancer which was not confirmed as a primary tumor, of non-Tunisian origin. The kits IL10, IL22 and IL23 are the Diaclone brand. The dosage of interleukins was based on two techniques, the first was the Sandwich ELISA for IL10, IL22 and IL23. The second was the solid phase chemiluminescent immu

nometric assay by the IMMULITE 1000 automated system for IL6, IL8, IL1β and TNFα.

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

After a check of the normality of the distribution via the shapiro-Wilk test in the event of the number of staff less than 50 or the Kolmogorov-Smirnov test if the number of staff exceeds 50. The comparative study, on independent series, was carried out using the Student's test for the quantitative variables and the Chi-square test for the qualitative 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 with extremes ranging from 24 to 82 years. Male predominance was observed with Male: Female ratio equal to 1.5 (Table 1).

Thirty-six percent of the patients had a family history of cancer, of which 59% had colorectal cancers. The most frequent tumor location was in the colon, 61.7% of cases, including 31.7% in the right colon and 30% in the left colon. thirty-eight point three percent of cases were localized to the rectum. The most frequently observed stage was stage IV (41.7% of cases), followed by stage III (35% of cases), then stage II (21.6% of cases) and stage I (1.7% of cases). Metastases were localized to the liver in 60% of cases (Table 1).

Table 1: Clinical data of patients with CRC

Characteristics	Number of patients (n=60)	Frequency (%)
sex		
man	36	60
Women	24	40
Age: average 58 years old (24-82 years old)		
20-29	2	3.3
30-39	3	5
40-49	12	20
50-59	14	23.3
60-69	14	23.3
>70	15	25
Personal risk factors		
Alcohol	2	3.3
Tobacco	16	26.7
Ulcerative colitis (UC)	0	0
Crohn's disease	0	0
other	22	36.7
Family history of cancer		
CRC	13	21.7
Other	9	15
Location of the tumor		
Left colon	18	30
Right colon	19	31.7
Rectum	23	38.3
The TNM stage of disease		
Stage I	1	1.7
Stage II	13	21.6
Stage III	21	35
Stage IV	25	41.7
Metastasis Location		
Liver metastases	15	60
Other	10	40

According to the TNM classification, the majority of patients were stage T3 and T4 (91.6% of cases). Stage N1 lymph node involvement was observed in 42% of cases. The search for RAS status was carried out in 20 patients, of which 13 patients had a mutated RAS status and 7 cases a wild RAS status (Table 2). Among the 60 patients, 18 patients (30% of cases) had vascular emboli (EV) and 13 patients (21.7% of cases) had perineural sheaths. For pro-inflammatory cytokines, the mean concentrations were for IL1β, IL6, IL8, IL23, TNFα respectively 1.13 ± 3.34 pg/ml (0 to 15.7 pg/ml), 12.29 ± 18.7 pg/ml (0 to 117 pg/ml), 61.9 ± 159.71 pg/ml (0 to 1173 pg/ml), 1.87 ± 7.14 pg/ml (0 to 44.57 pg/ml), 8.3 ± 4.9 pg/ml (0 to 27.2 pg/ml). For anti-inflammatory cytokines, the mean concentrations for IL10, IL22 were respectively 0.93 ± 5.23 pg/ml (0 to 39.35 pg/ml) and 22.1 ± 27.35 pg/ml (4.2 to 148.61 pg/ml) (Table 3).

Table 2: Histological data of patients with CRC

T stage of tumor	n	%
T1-T2	5	8.4
T3-T4	55	91.6
Lymph node involvement (N)		
N0	21	35
N1	25	41.7
N2	10	16.7
Metastasis (M)		
M0	35	58.3
M1	25	41.7
The TNM stage of disease		
I-II	14	23.3
III-IV	46	76.7
RAS Status		
Wild	7	11.7

Mutated	13	21.7
Not realized	40	66.6

Table 3: Summary table of the biological assay of pro and anti-inflammatory cytokines

Cytokine in pg / ml	Number of patient	Minimum value	Maximum value	Mean	Ecart type
IL6	60	<2	117	12.26	18.7
IL10	60	0	39.35	0.93	5.23
TNFα	60	<4	27.2	8.3	4.9
IL8	60	<5	1173	61.9	159.71
IL1β	60	<5	15.7	1.13	3.34
IL22	60	4.17	148.61	22.1	27.35
IL23	60	0	44.57	1.87	7.14

Our results showed that the concentration of IL1β increased in young patients under 45 years compared to those over 45 years (p = 0.01) (Figure 1). The IL1β level was higher with a statistically significant difference in the presence of vascular emboli (p = 0.013) (Figure 2).

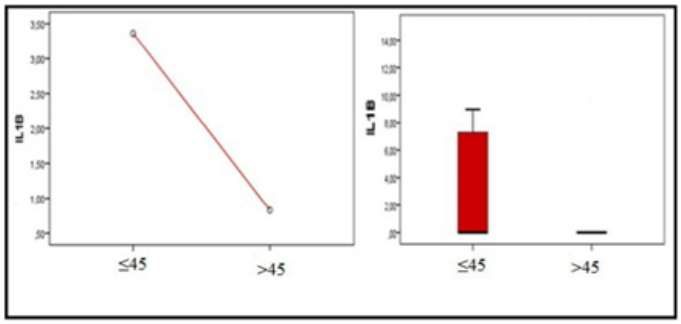

Figure 1: Correlation graph between serum Interleukin (IL)1 β levels in pg/ml and age

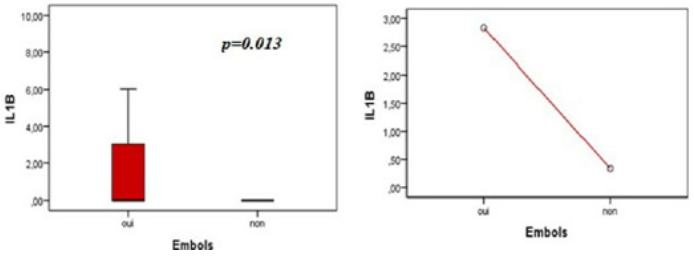

Figure 2: Correlation between serum Interleukin (IL)1 β levels in pg/ml and vascular emboli

Elevated serum IL8 was significantly correlated with poor prognosis: Our results showed a statistically significant relationship between the circulating level of IL8 and the stages of the disease (p=0.002) (Figure 3) with significantly higher levels for stage IV (p=0.000), and more particularly for those with mutated RAS status (p=0.001). A positive correlation was also found between IL8 and tumor markers; ACE (p=0.027) and CA19-9 (p = 0.045) measured preoperatively.

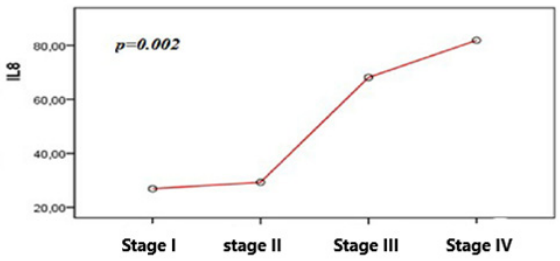

Figure 3: Kinetics of the IL8 curve according to the tumor stage

The serum IL6 level was very significantly higher in patients aged over 45 years (p=0.021) (Figure 4) and in those who had relapsed after adjuvant treatment (p=0.014). The mean IL10 concentrations varied depending on the T stage (p= 0.025), in fact, the highest concentrations were observed for the pT4 stages.

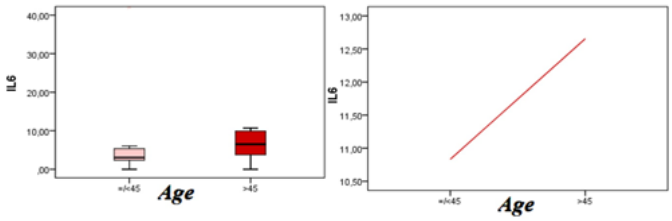

Figure 4: Correlation between serum Interleukin (IL) 6 levels in pg/ml and age

In addition, our results showed an increase in mean levels of IL22 for high-grade tumor differentiation (p= 0.032) (Figure 5).

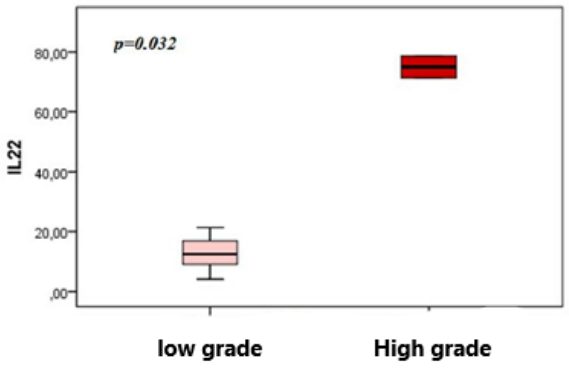

Figure 5: Correlation between serum Interleukin(IL) 22 levels in pg/ml and tumor differentiation grade

In our study, IL23 did not present any significance with any clinico-histo-pathological parameter. Also, it did not reveal any correlation with any cytokine studied.

For TNFα we observed higher concentrations of the serum level with the pT2 stages (p = 0.036). For the correlations between cytokines we found a statistically significant correlation between IL8 and IL6 on the one hand (r= 0.560 and p= 0.00001) and TNFα on the other hand (r= 0.404 and p= 0.001). A statistically significant correlation between pro-inflammatory

IL1β and anti-inflammatory IL10 (r= 0.279 and p= 0.021) (Figure 6).

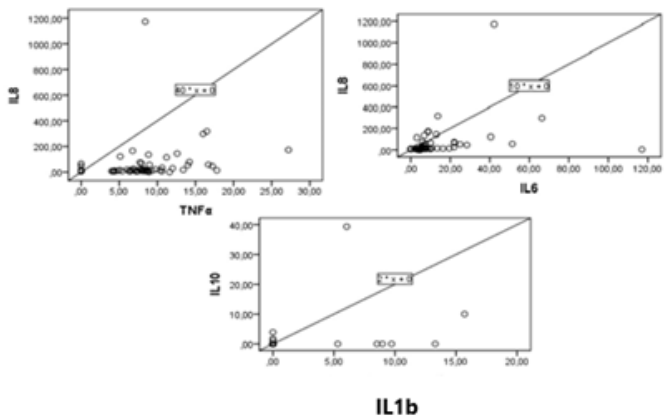

Figure 6: Correlation graph between serum cytokines profiles in pg/ml

Discussion

Recent data have shown that inflammation is an essential component in the process of carcinogenesis in CRC. Indeed, inflammation and cancer use similar developmental mechanisms, such as angiogenesis. The prolonged presence of inflammatory cells and their mediators (Inflammation Cytokines) in the tumor microenvironment has been shown to accelerate tumor growth and inhibit apoptosis of transformed cells [6]. Through this study we have tried to establish the relationship between cytokines of inflammation and the clinico-histopathological prognostic factors. TNF-α is a central pro-inflammatory cytokine contributing to malignant tumor progression in the tumor microenvironment. Indeed, some studies have shown that TNF-α is expressed more abundantly in CRC tissue than in the adjacent normal mucosa, and that its expression is positively correlated with advanced Dukes stages [7]. Another study carried out in Saudi Arabia showed that the presence of high expression of the TNF-α gene in colorectal cancer cells is strongly correlated with advanced stages of the tumor [8]. In our study, there wasn't significant difference in mean concentrations of TNF-α according to the stages of the disease but we observed that the level of TNFα varies according to the stage T (p= 0.036) with higher concentrations observed for pT2 stages. IL-1β is a major "alarm" as a pleiotropic pro-inflammatory cytokine. It acts essentially by inducing cascades of cytokines and mediators promoting inflammation. It is produced by both malignant cells and environmental micro cells contributing to the initiation and development of these cancers associated with inflammation, including gastrointestinal tumors [9,10].

In our study, we observed a significant difference in mean concentrations of IL1β according to the age (p = 0.01), the highest concentrations were observed in younger patients under 45 years. This can be explained by the important role of this cytokine in the growth and invasion of colon tumors by activating the property of self renewal of stem cells colic (CSC) and the tumor microenvironment (TME) [10]. It was shown by a meta-analysis of 91 studies published in 2013 that IL1β was associated with a poor prognosis in patients with colorectal cancer [11]. This was agreed with our results, in which the mean IL1β concentrations were significantly higher in patients with positive vascular emboli (p = 0.013), this constitutes a factor of poor prognosis.

IL-6 is a pleiotropic cytokine with a wide range of biological activity in immune regulation, hematopoiesis, inflammation and oncogenesis. several studies suggesting an important role of IL-6 in the initiation of the tumor and the progression of various cancers, in particular colorectal cancer [12]. They also demonstrated that high levels of IL-6 is correlated with poor prognosis in CRC. Indeed, it was reported that the high expression of serum IL-6 was associated with an increased risk of CRC [12]. These data are in agreement with our results which were found significantly higher levels of IL-6 in patients older than 45 years which is the largest population risk of developing CRC. Our results also showed a significant correlation between elevated levels of serum IL-6 and relapse occurred (p = 0.014). These results were reported in the study published by Olsen J, et al. which demonstrated that IL6 is positively regulated in tumor tissue at the transcriptional level and is significantly associated with an increased risk of relapse [13]. Therefore IL6 can be used as an indicator of relapse.

IL-8 is a pro-inflammatory chemokine produced by various types of immune cells. The acquisition of IL-8 and/or its receptors CXCR1 and CXCR2 is known to be a relatively common phenomenon during tumor progression. Indeed, several studies have shown that IL-8 and its receptor CXCR2 are two of the most positively regulated chemokines in colorectal cancer [14]. A meta-analysis including a total of 18 eligible studies evaluating the impact of IL-8 expression on colorectal cancer prognosis and its clinico-pathological characteristics suggested that overexpression of IL-8 is significantly associated with a poor prognosis in colorectal cancer [15]. These data were also found in our study. Indeed, we observed that the IL8 level increased progressively with the stage of the disease (p = 0.002), in particular with metastatic stage (p = 0.000), the mutated RAS status (p = 0.001), the high rate of ACE (p = 0.027) and CA19-9 (p = 0.045) which are known factors of poor prognosis. Considering these results we conclude that IL-8 may be considered as a biomarker with poor prognosis.

IL10 is a multifunctional immunosuppressive and anti-angiogenic immunoregulatory cytokine. However, the role of IL-10 in colorectal cancer remains ambiguous. Indeed, a study by Stanilov N, et al. reported that the level of IL-10 was significantly higher for patients with colorectal cancer compared to control subjects, contrary to the results demonstrated by Abtahi Sh and al who state that the level of IL-10 was significantly lower in patients with colorectal cancer compared to healthy subjects [16,17]. The association between the level of IL-10 and clinical and histological prognosis factors was not well studied, which explains the controversial results of several studies. In our study, we observed a significant difference in mean IL10 concentrations depending on the T stage (p=0.025) with higher concentrations for the advanced stages pT4. This is in accordance with the results of Abtahi Sh, et al. who had shown that the concentration of IL10 increases with the advanced stages and the study by Sakamoto T, et al. which had shown that the prognosis of patients expressing IL-10 was significantly worse compared to those who didn't express IL-10 [17,18]. Other studies in Tunisia have shown a significant association between high serum levels of IL-10 and advanced stages of the disease. [19]. The IL22 is a cytokine family IL-10 produced by T cells and innate lymphoid cells. The signaling pathway orchestrates the immune defense and tissue regeneration through pleiotropic effects.

Recently, the role of IL-22 in tumor models of colon cancer has been tested during different phases of carcinogenesis; the results suggest that an increase in IL22 levels may lead to tumor progression [20]. This is consistent with our results which showed an increase in mean IL22 concentration in patients with a high grade of differentiation. Some studies have also shown that overexpression of IL22 stimulates tumor progression in lung, skin and other cancers [21]. On the other hand, they aren't overexpressed in the event of a hepatic tumor [20]. This may explain our results, where we found that the IL22 level was higher in patients with extrahepatic metastases (pulmonary, bone, etc.).

Recent studies have shown that IL-23 plays an essential role in the pathogenesis of inflammatory bowel disease (Crohn's disease, ulcerative colitis)

and colon cancer associated with colitis [22]. This may explain the negative results in our study of IL23 with respect to clinicohistopathological prognostic factors since nobody of our patients had chronic inflammatory bowel disease. Our results showed a strong positive correlation between IL8 and IL6. We also found that IL8 was associated with poor prognostic factors; clinical and histopathological; in particular the metastatic stage (p= 0.001) and the mutated RAS status (p= 0.001). On the other hand, IL6 was significantly associated with the occurrence of relapse (p= 0.014). This may lead us to conclude that IL-8 may be a prognostic biomarker of aggression although IL-6 may be a predictive biomarker of relapse.

In our study, we found a positive correlation between TNFα and IL8 which is not contradictory with the data in the literature which show that the secretion of IL8 can be induced by TNFα. This allows us to deduce that TNFα is the main precursor of IL8 production in CRC. TNFα was also associated with early stages T2; so it might be a useful biomarker for CRC screening in early stages.

In addition, we found a positive correlation between IL10 and IL1β which are also correlated with aggressive stages including T4 stages for IL10 and vascular invasion for IL1β. In addition IL-22 which is a cytokine of the IL-10 family; was associated with a high grade of differentiation and an extrahepatic metastatic stage.This can lead us to deduce that IL1β, IL10 and IL22 can be indicators of the aggressiveness of CRC and therefore biomarkers of poor prognosis implying a more intensive therapeutic management.

Conclusion

In conclusion, TNFα, IL1β, IL6, IL8, IL10 and IL22 could be considered potential prognostic biomarkers in colorectal cancer by identifying patients with poor prognosis requiring aggressive treatment, patients at high risk of recurrence requiring closer monitoring and a new prognostic score could also be identified from these simpler and more accurate serum biomarkers. These cytokines could help the clinician to indicate the appropriate treatment and could also be therapeutic targets. Nevertheless, we are aware that this work requires other clinical studies with a larger number and over a longer period to better understand the inflammatory profile and its correlation with CRC and the particularity of Tunisian patients and to validate the prognostic value of these serum bio-markers.

Conflicts of Interest

The authors declare no conflict of interest.

What is known about this topic

- Inflammation plays an important role in carcinogenesis in colorectal cancer.
- The tumor microenvironment is an essential element participating in the neoplastic process thanks to cytokines, promoting proliferation, survival and migration.
- IL1β is associated with a poor prognosis in patients with colorectal cancer.

What's new from your study

- The IL22 level was higher in patients presenting extrahepatic metastases (pulmonary, bone, etc.).
- TNFα was also associated with early T2 stages; thus it could be a useful biomarker for the screening of CRC at early stages.
- TNFα, IL1β, IL6, IL8, IL10 and IL22 could be considered potential prognostic biomarkers in colorectal cancer.

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