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Evaluation of hepatotoxicity induced by colorectal cancer chemotherapy in an Algerian population

Haoud Khadidja*, Mellali Sarah, Kerouaz Lilia, Merhoul Fatima Zohra, Kebir Rajaa

Department of Biology, Faculty of Natural and Life Sciences, Djillali Liabes University, Sidi Bel Abbès, Algeria

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Abstract

Colorectal Cancer (CRC) is a malignant tumor that originates in the cells of the colon or rectum. Chemotherapy, alone or combined with other treatments, have largely contributed to the improvement of the survival of the patients, however their side effects can appear at any time in particular liver damage. The objective of our study was to evaluate the toxicity of treatments used in chemotherapy of CRC, and more particularly to determine their hepatotoxicity. For this purpose, we carried out a retrospective analytical epidemiological study, going from February to May 2019, including 109 patients with CRC and undergoing anticancer chemotherapy at the Anti Cancer Center (CAC) of Sidi Bel Abbes. Our patients developed hepatotoxicity in 43.04% of cases, resulting in increased levels of liver parameters, transaminases, alkaline phosphatase, gamma GT, total and direct bilirubin's. Our work suggests that the anti-cancer therapies used may be responsible for hepatotoxicity; This shows that dosage adjustment and established prevention measures are insufficient.

* **Corresponding Author:** Dr Haoud Khadidja ✉ haoud_khadidja82@yahoo.fr

Introduction

Colorectal cancer (CRC) is the most common digestive malignant tumour,it is the second leading cause of cancer-related death in Western countries (Haggar and Boushey, 2009). Every year, 500,000 people with CRC die around the world and one million new cases are diagnosed (GLOBOCAN, 2000). The five-year survival rate of CRCs is in the range of 40-60%, and the main cause of death is the occurrence of metastases (Abdalla *et al.,* 2004; Fernandez *et al.,* 2004; Pawlik *et al.,* 2005).

Cancer therapy has substantially improved over the past decade with the introduction of combination drug regimens, adjuvant and targeted therapies. Combination chemotherapy is the mainstay of treatment for most cancer, either alone or in combination with surgery and radiotherapy. Sequential studies of combinations of cytotoxic drugs have resulted in improvements in the outcomes for cancer (Makin, 2018).

Chemotherapy agents are often given at regular intervals called cycles. In the management of CRC, First-line chemotherapy combining fluoropyrimidines (5-FU, or oral fluoropyrimidines) with Oxaliplatin (Folfox and Xelox-type regimens) or irinotecan (Folfiri-type regimens) provides response rates of 48-56% and a median survival of 16-22.4 months in patients with advanced disease (de Gramont *et al.*, 2000; Douillard *et al.*, 2000; Tournigand *et al.,* 2004). Cetuximab and Panitumumab are monoclonal antibodies to the epidermal growth factor receptor (EGF-R). Cetuximab is effective in combination with Irinotecan or monotherapy in patients with metastatic CRC resistant to Irinotecan (Cunningham *et al.*, 2004). However, due to the low specificity of chemotherapeutic agents, its adverse reaction and toxicity are commonly observed during chemotherapeutic treatment to cancer patients, which largely affect its efficacy and application as patients are normally intolerable to the side effects caused by chemotherapeutic agents (Allemani and Coleman, 2017). The side effects of chemotherapy can be considerable, and it is important to educate and monitor the patients carefully during treatment. Toxicities vary according to the specific agent, dose, route and schedule of administration and any predisposing patient factors, which may be known or unknown. Apart from nausea and vomiting and acute cholinergic gastrointestinal effects, most common toxicities occur because of the cytotoxic effects on normal dividing cells (Dickens and Ahmed, 2018). Because the therapeutic dose is close to the toxic dose in this group of drugs, errors in dosage calculation carry a high risk of acute and cumulative toxicity, which increases the likelihood of mortality in patients (Bubalo *et al.,* 2014; Goldspiel *et al.*, 2015).

Although few medication errors harm the patient, they are the second most common cause of death in patients undergoing chemotherapy (Mattsson *et al.,* 2015). Chemotherapy drugs can cause a variety of liver damage. Among them, platinum drugs such as Cisplatin and Oxaliplatin can greatly damage the ability of the sinusoidal liver and destroy the blood vessels that transport oxygen to the liver (Mikalauskas *et al.*, 2011). Hepatotoxicity limits the duration of treatment and dosage of drugs for cancer patients (McWhirter *et al.,* 2013).

The liver toxicity of CRC chemotherapy and its complications are poorly evaluated (Baumgaertner *et al.,* 2010). For this reason, we have proposed to evaluate the toxicity of chemotherapy drugs, particularly on metabolic functions of the liver in patients with CRC.

Material and methods

We carried out a retrospective analytical epidemiological study at the medical oncology department of the Centre Anti Cancer (CAC) of the wilaya of SidiBel Abbes. This study took place from February to May 2019.

Study population

The subjects admitted to this study are patients with CRC and recruited retrospectively from the oncology department. We recruited 109 patients (64 men and 45 women) with ages ranging from 23 to 81. Included

in this study were: Patients with CRC, deceased and not deceased, not undergoing other treatments with hepatotoxic effects, and not with a history of liver pathology. Excluded were patients with colorectal metastatic localization of another type of cancer, patients with inflammatory and ischemic metabolic diseases and patients with less than 4 cycles of chemotherapy.

Data collection

The demographic and bioclinical data were obtained from the patient file and we developed a patient information sheet, which we collected: Age, Sex, Situation, Size, Weight, Body Mass Index (BMI), Results of additional examinations: endoscopic, biological, anatomopathological and medical data: type of neoplasia, personal, family, surgical history, habits and type of treatment. An average of 4 cycles of chemotherapy was chosen for each patient.

Biological tests

A biological examination including a liver, kidney and blood test was performed prior to any treatment: Alanine Aminotransferases (ALT), Aspartate Aminotransferases (ASAT), *Alkaline phosphatase* (PAL), *gamma-GlutamytTransferase* (GGT), Bilirubin total and direct, Urea, creatinine, Blood Count Formula (NSF). The normal rate of the biological parameters studied was:- ALT :< 35 UI/L - AST : < 37 UI/L- GGT: 4-35 UI/L - ALP: 98-279 UI/L- Total Bilirubin: <10 mg/L - Directe Bilirubin : < 8 mg/L- Urea : 0,1 - 0,5 g/L - Creatinin: 4 - 14 mg/L

Statistical analysis

Statistical data capture and analysis was performed using software: Microsoft Office Excel 2007, IBM® Spss®statistics IBM Corp (version 20.0).

The results were expressed as a percentage for the qualitative variables and as the mean standard deviation of the mean for the quantitative variables. Frequency, mean and median was calculated as well as the khi2 test for qualitative comparison. Comparison between groups is done with the Student test.

The link between the qualitative variables was made with the Pearson Khi two test, the value of P less than or equal to 0.05 was considered significant. The results are given in tables and histograms.

Results

The characteristics of our patients are shown in Table 1.

Table 1. Characteristics of the patients.

Characteristics	Effectif	Rate
Sex		
Men	64	58,7 %
Women	45	41,3 %
Sex ratio	1,42	
Age (year)	56,10 ±14,32	
Weight (kg)	62,76±12,85	
Tumor location		
Colon	84	77,1 %
Rectum	24	22,0 %
Colorectal	1	0,9 %

The different protocols administered for the different CRC treatments of patients are reported in Table 2. The age range [50-59] was the most affected with 24.8% of cases, followed by the age group [40-49] which represents 23.9% of cases. Patients under 29 years of age accounted for only 2.8% of cases (Figure 1). For body mass index (BMI), only 5 patients (4.6%) had a BMI greater than 30 Kg/m², 24 patients (22% of cases) were overweight, and 15 patients (13.8% of cases) were underweight (Figure 2).

Table 2. The different protocols administered for the patients.

Treatement	Patients	
	n	Rate
XELOX	50	45,9 %
XELOX + Bevacizumab	13	11,9 %
XELODA	9	8,3 %
FOLFOX 4	8	7,3 %
FOLFIRI	6	5,5 %
FOLFOX + XELOX	4	3,7 %
FUFOL	3	2,8 %
XILIRI	3	2,8 %
Cisplatin	3	2,8 %
LV5FU2	2	1,8 %
Panitumumab + Xelox	2	1,8 %
Bevacizumab + Irinotecan	1	0,9 %
Bevacizumab + IFL	1	0,9 %
Irinotecan + 5FU + FolinicAcid	1	0,9 %
FOLFIRI + XELOX	1	0,9 %
Cetuximab + Irinotecan + Bevacizumab	1	0,9 %
FOLFIRI + Bevacizumab	1	0,9 %

The relationship between tumour site (Table 1) and sex is statistically significant with a value of p=0.044.

The distribution of patients by tumour histological type is shown in Figure 3, the degree of differentiation is shown in Table 3. Of the 109 patients recruited for our study, 47 (43.12%) had variations in parameters demonstrating liver involvement (Figure 4).

Transaminases (ALT, AST and GGT)

The average rate of transaminases remains in the norm before treatment and during the first three cures (40IU/L). However, we noted an increase in mean transaminase rates after the fourth cycle of chemotherapy; for example, TGO increased from (32.37 IU/L to (42.02 IU/L) and TGP from (25.27 IU/L) to (27.86 IU/L) (Figure 5).

The GGT rates showed an increase from the second course of treatment, thus exceeding the standards (35 IU/L). This rate increases from (41.58 IU/L) to (46.87 IU/L) during the third treatment and from (46.87 IU/L) to (49.76 IU/L) during the fourth treatment.

ALP (Alkaline Phosphatase)

The mean ALP rate remained within the standards (279IU/L) during the four rounds of chemotherapy, with a slight increase from the second cycle which averaged (221.43IU/L) to (285.18 IU/L) (Figure 6).

Mean levels of bilirubin (10 mg/L total bilirubin, 8 mg/L direct bilirubin) remained within standard during the first three cures (Figure 7), with moderate elevation after the fourth cycle.

We noted a proportional relationship between disruption of liver function and the following treatments:

• XELOX /AST and FOLFIRI/AST with significant values of P= 0.049 and P= 0.047 respectively.

• XELOX + Bevacizumab/ALT and XELODA/ALT with significant values of P= 0.046 and P= 0.022 respectively.

• XELOX+Panitumumab/GGT and XELOX+ FOLFOX/GGT with significant values of P= 0.020 and P= 0.015 respectively.

• FOLFIRI and total bilirubin with a value of P=

0.047.

Discussion

The average age of our patients was 56±14.32 years for both sexes. This shows, on the one hand, that the CRC affects both men and women alike and, on the other hand, the increase in its appearance with the increase in age. These observations are similar to those of Maamri (2015) and Tebibel *et al.* (2014), all of which have shown that an aging population contributes to the increased incidence of cancer.

A study on colon cancer, carried out by the digestive cancer registries of Côte-d'Or and Calvados (Belot *et al.*, 2008) shows that the frequency of advanced stages (stage IV) increases with age.

Table 3. The histopathological data of tumors.

Type	Patients (n)	Rate
Well-differentiatedadenocarcinoma	78	71,6
Moderatelydifferentiatedadenocarcinoma	14	12,8
Poorlydifferentiatedadenocarcinoma	6	5,5
Carcinoma	11	10,1

It can be explained by its discovery usually at a late stage because of a delay in consultation, inherent essentially the negligence or ignorance of the first signs of call and this by lack of awareness and/or information (Arfa *et al.*, 2006; Ballinger and Anggiansah, 2007).

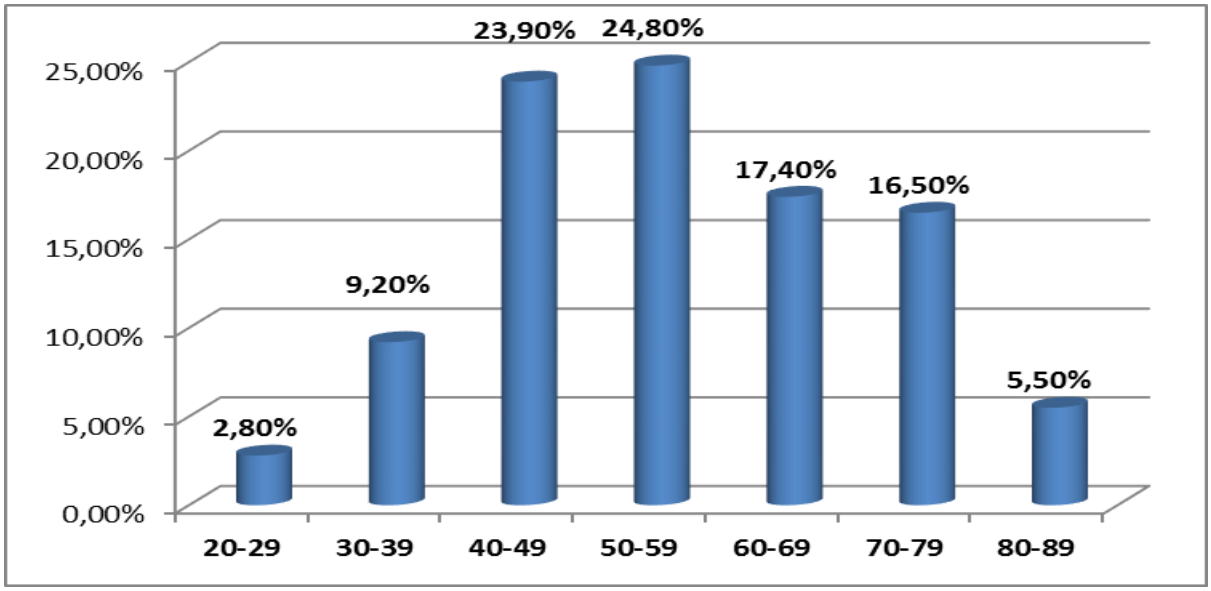

Fig. 1. Distribution of patients by age range.

In our series, there was a male predominance with 59% of cases, or a sex ratio (M/W) of 1.42. These data are similar to the retrospective study Tebibel*et al.* (2014), Benelkhaiat *et al.* (2010), Amegbor *et al.* (2008) and Letonturier (2008), all of which reported male predominance. In our study, BMI analysis found that 22% of patients were overweight and 4.6% were obese. Overweight and obesity have already been convincingly associated with the risk of CRC. Indeed, the mechanisms involved are the increase in endogenous levels of certain hormones and growth factors (insulin, sex hormones, leptin, insulin-like growth factor-1 [IGF-1]) who are involved in biological functions that play an important role in carcinogenesis (Zheng *et al.*, 2018).

Among the different tumour sites, the colon is the most common (77%) (Without specifying the

topographical distribution because it was not reported in all of our patients' records, followed by the rectum (22%), only one case had a double colic and rectal localization (1%). These data are similar to those of Tebibel *et al.* (2014), which reported a predominance of colic cancer over rectal cancer.

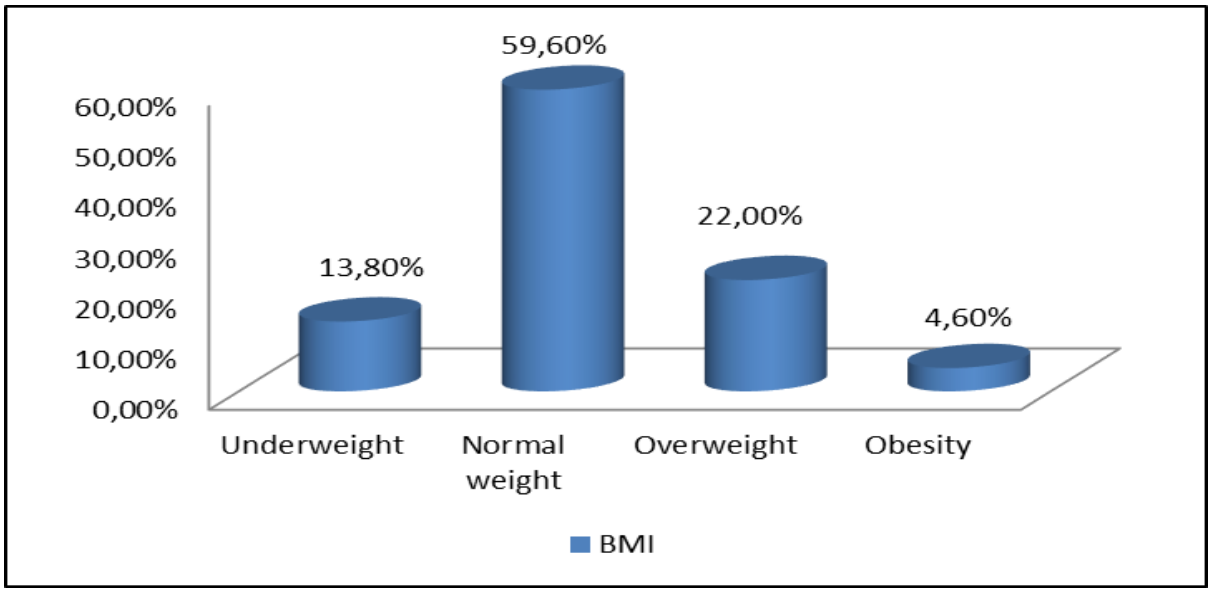

Fig. 2. Patient distribution according to BMI (the Body Mass Index).

In our series, lieberkuhnian adenocarcinoma was the most common histological form with 71.6% of all adenocarcinomas, followed by colloid adenocarcinoma representing 18.3% of cases and signet ring cell carcinoma 10.1%.Our results are comparable to those of Housse *et al.* (2015) and S. Tebibel *et al.* (2014) who reported a predominance of lieberkuhnian adenocarcinoma over colloid adenocarcinoma.

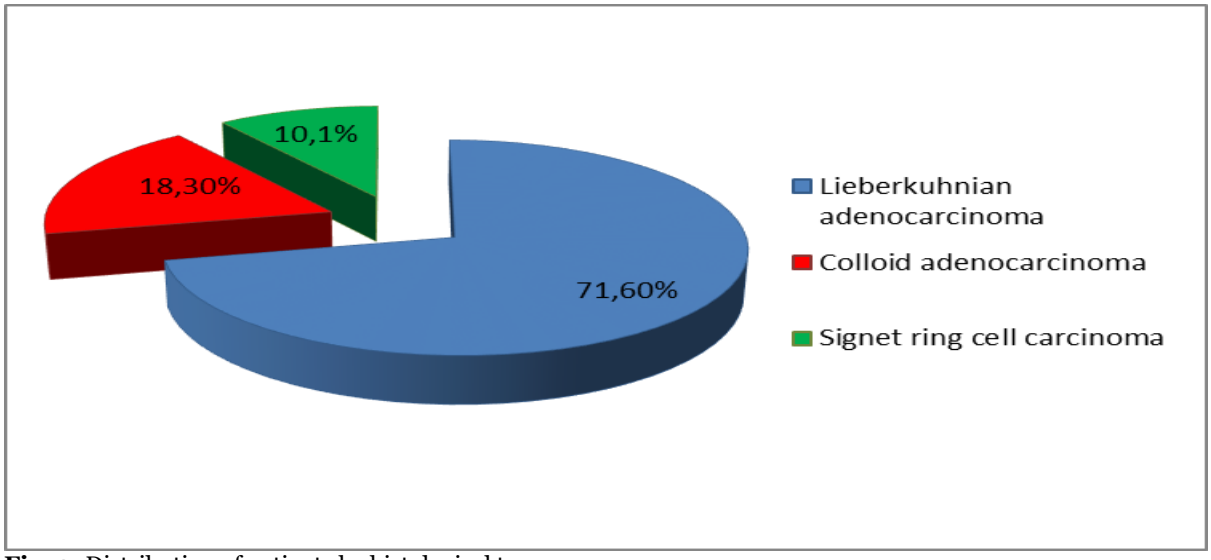

Fig. 3. Distribution of patients by histological type.

The cytopathological study showed that well differentiated adenocarcinomas were predominant in our series, they represented 71.60%, followed by moderate and little or no differentiated forms with respective frequencies of 12,80% and 15.60% of our population. These results are similar to those of S. Tebibel *et al.* (2014) which demonstrated that the well-differentiated form was dominant, or 83.85% of

the cases, followed by little or no and moderately differentiated forms with respective frequencies of 13.43% and 2.99%.

The toxic effects of chemotherapy vary according to the drugs used, the dosage, the patient and from one chemotherapy cure to another. They are not always systematic.In our systematic analysis, we found that the values of ALT, AST, GGT, ALP, total and direct bilirubin were higher than the standards, our results are similar to those of Desjardin (2014), Chaput *et al.* (2008) and Gambiez (1999) who demonstrated that for transaminases, ALP and GGT, the threshold of twice the high laboratory standards was selected as significant for hepatic impairment. The majority of our patients had chemo-induced hepatotoxicity which explains hepatocytolysis leading to intense release of liver enzymes that gain the general blood circulation.

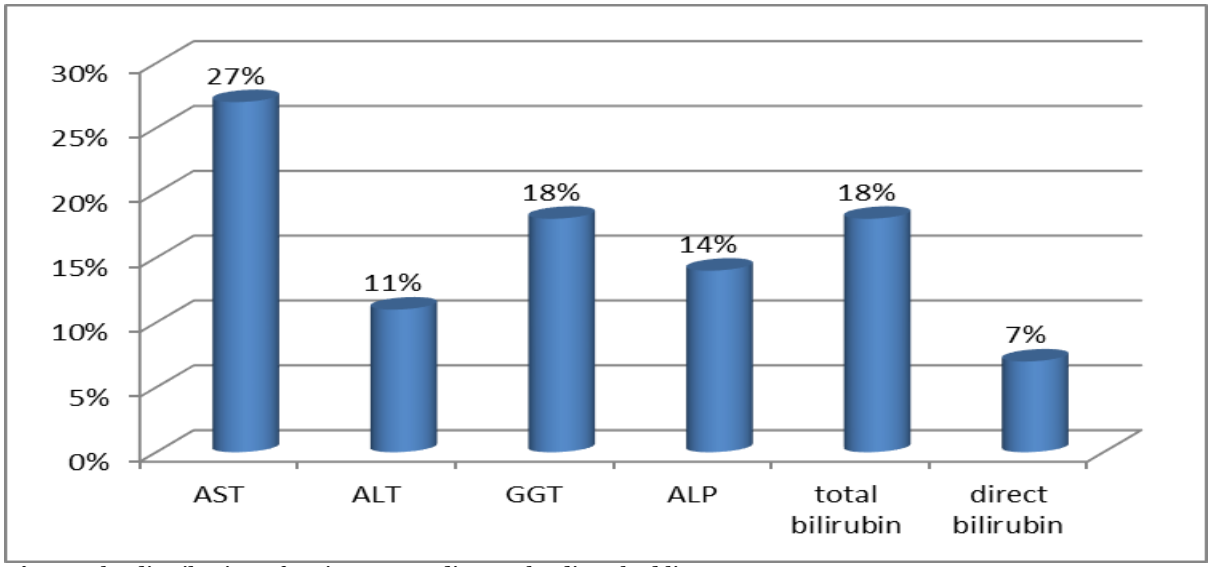

Fig. 4. The distribution of patients according to the disturbed liver parameter.

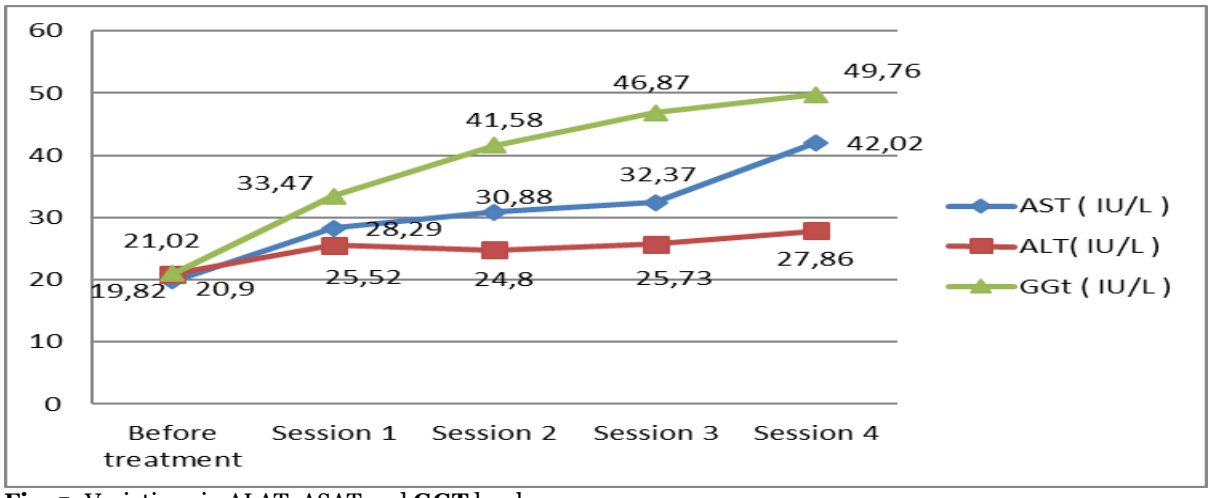

Fig. 5. Variations in ALAT, ASAT and **GGT** levels.

The use of different types of drugs in CCR chemotherapy protocols is a leading cause of hepatotoxicity, with some drugs known to have toxic effects on the liver. Chemotherapy combining 5-FU with oxaliplatin and/or irinotecan causes hepatotoxicity of healthy parenchyma (Grenet, 2018). Oxaliplatin hepatotoxicity is mediated by excessive production of reactive oxygen species, which results in accumulation of lipid vesicles in the hepatocytes (Kandutsch *et al.,* 2008). Our results are consistent with those of R. Arotcarena*et al.* (2006) who demonstrated that elevated levels of GGT and ALP

were a suggestive element of oxaliplatin hepatotoxicity. Another study by Brouquet*et al.* (2009) in 146 patients treated with 5-FU alone, FOLFOX, FOLFIRI, or both successively, demonstrated that GGT levels greater than 1,5N in preoperative was predictive of sinusoidal lesions.

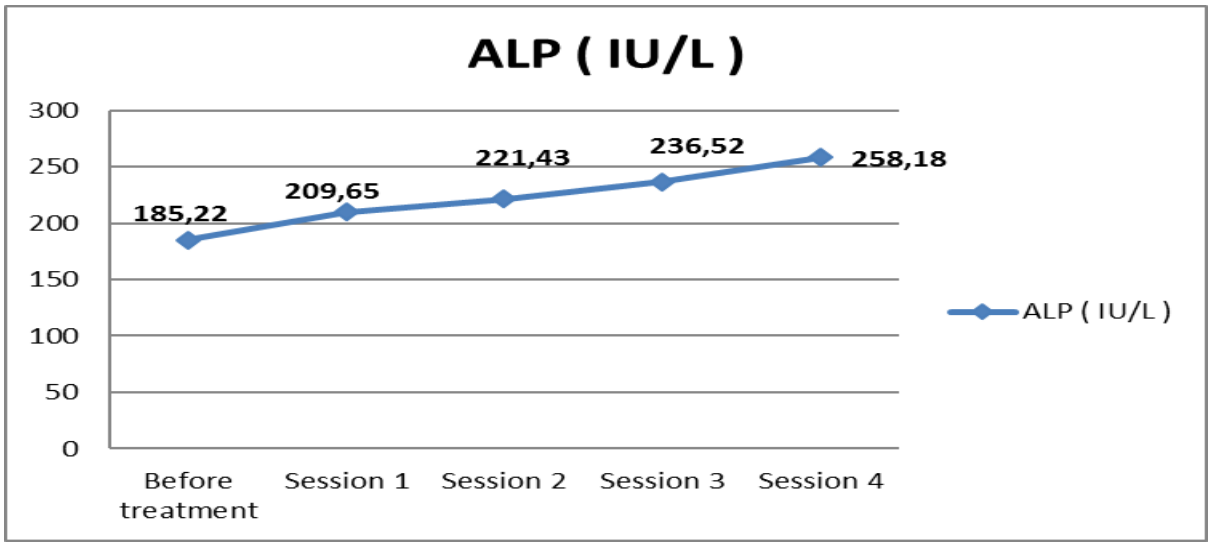

Fig. 6. Variations in ALP levels.

Oxaliplatin chemotherapy protocols (XELOX, XELOX + Capecitabin, XELODA and FOLOX) that are associated with 5-FU are potentially more toxic.In our study, we noted a predominance of the XELOX protocol used in 46.6% of cases. In 2001, FOLFOX 4 demonstrated efficacy in 2246 patients, 60% of whom were stage III, but its toxicity was increased (Vargas *et al.,* 2014). The study of Tournigand *et al.* (2004), which incorporated oxaliplatin and irinotecan in the treatment of advanced CRC, showed that there was a therapy-related death associated with Folfox andFolfiri due to haematotoxicity.

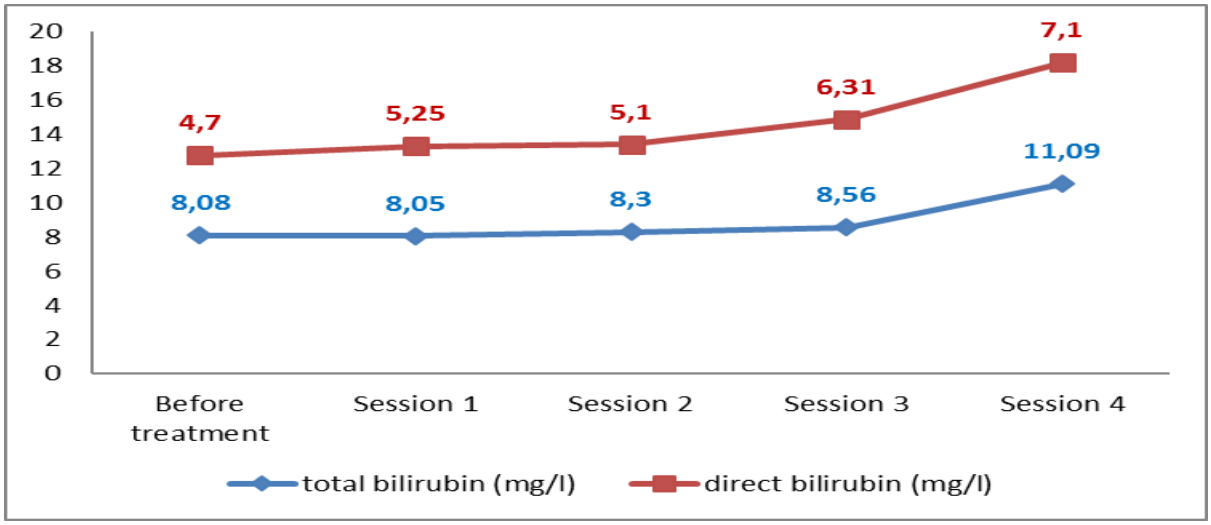

Fig. 7. Variations in Bilirubin (total and direct).

The Phase III and randomized clinical trials showed survival benefits in patients receiving oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) combined with 5-FU/LV compared to 5-FU/LV. As a result, FOLFOX and FOLFIRI have become advanced CRC primary chemotherapy. Several other agents were subsequently approved for treatment in combination with FOLFOX or FOLFIRI. These include

Capecitabin, Bevacizumab and Cetuximab (*Chen et al., 2016).*

The results we obtained confirm reversible and not chronic hepatotoxicity in the majority of cases.It has been found that the different CRC chemotherapy protocols based on Oxaliplatin and irenenotin and 5-FU are the most likely to disrupt liver parameters. These variations are indicative of secondary hepatic impairment induced by these anticancers.

Conclusion

Hepatotoxicity secondary to cancer treatment is not a common but serious side effect due to the liver being an organ involved in drug metabolism. Through this work, we found that more almost half (43.12%) of the patients treated for a CRC developed chemo-induced hepatotoxicity.

The purpose of our study was to evaluate liver endpoints (ALT– AST – ALP – GGT – total and direct bilirubin) in patients undergoing CCR chemotherapy. Our results showed elevations in the levels of the different hepatic biochemical parameters. The main drugs used in the different chemotherapy protocols and responsible for this hepatotoxicity are XELOX, FOLFIRI, XELODA, XELOX/Bevacizumab, XELOX/Panitumumab and XELOX/FOLFOX. The molecules common to all these treatments are L'Oxaliplatin, L'Irenotecan and 5-FU known to cause hepatotoxicity *(Chen* al., *2016)*. Chemotherapy has been shown to affect liver function, which is determined by the duration of treatment. Thus, the type and dose of cancer drugs are the main factors of disruption of liver function, leading to secondary liver diseases (viral hepatitis, liver failure...) and can be chronic. They can be limited or avoided through preventive or curative treatments and practical advice.

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