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Peripheral Blood Cytokines Levels in Senegalese Women with Cervical Cancer during Chemotherapy

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Abstract

Cervical cancer is the leading cause of cancer deaths of women in developing world. Several studies demonstrated evidences of inflammatory cytokines implication in cancer progression including in initiation, promotion and invasion by affecting the immune surveillance. Our aim was to measure blood circulating pro- and anti-inflammatory cytokines levels, their profiles according to treatment issue and relation with prognostic factors in cervical cancer during chemotherapy. Blood samples were collected from a cohort of 35 cervical cancer women and 42 women healthy controls (HC) with no history of malignancy. For each CP, three samples were taken at three-week intervals. The first one (S1) was taken before initiation of the chemotherapy protocol. S2 and S3 were samples collected respectively at day 21 and day 42. Cytokines levels were evaluated by ELISA. Mean age of patients was 54.1 year (35 - 77 yo). In groups, no relation was observed between age and cytokines levels. Before chemotherapy, high levels of IL-6, IL-4 and IFN-γ were observed in CP compared to HC ($p < 0.001$) and at the same period, IL-10 and TNF-α levels were significantly low in CP ($p < 0.05$) and negatively correlated ($r = -0.79$; $p = 0.017$). In this CP group, IL-4 levels were positively correlated between S1 and S2 ($r = 0.72$; $p = 0.002$) and between S1 and S3 ($r = 0.74$; $p = 0.019$). Similar correlations were observed for TNF-α levels: S1/S2 ($r = 0.54$; $p = 0.027$), S2/S3 ($r = 0.82$; $p = 0.009$) and S1/S3 ($r = 0.66$; $p = 0.036$) with a significant increase of TNF-α in blood during treatment. Depending on chemotherapy's efficacy, CP patients were separated into 1) non responders (NR), 2) partial responders (PR) and 3) good responders (GR). Compared to PR and

GR groups, NR patients showed: a) higher serum levels of IL-6, IL-10 and IFN-γ during the follow-up and b) lower serum levels of IL-4 and TNF-α. In addition, serum levels of IL-4 were significantly higher in GR patients however TNF-α was the predominant cytokines in PR group. Our results highlight the variation of circulating cytokines such as IL-6, IL-10 and IFN-γ during cervical cancer chemotherapy. In addition, this study suggested that IL-4 and TNF-α might represent potential biomarkers candidate in cervical cancer. Applications in cancer management need further investigations particularly about the relevant prognostic indicator following chemotherapy and validation studies must provide more assurance for translation into clinical practice.

Keywords

Cervical Cancer, Chemotherapy, Cytokines, Biomarkers

1. Introduction

Cervical cancer is one of the most common tumors among female in the world [1], and tragically, is a 1st leading cause of cancer death for women especially in the developing countries [2]. In Senegal, it is estimated that there will be 1876 new cases and 1367 deaths from cervical cancer in 2018 [3]. The devastating situation of cervical cancer in Senegal is not limited to the high incidence and mortality rate of the disease, but also of greater concern is low level of awareness of ways to prevent a woman from having cervical cancer which could be thought primary prevention (Human Papilloma Virus vaccine) and secondary prevention (cervical cancer screening). This is quite critical because of limited infrastructure for effective treatment for invasive cervical cancer particularly when diagnosed in late stages. Treatment of women with cervical cancer is largely dependent on the stage of cancer [4]. Presently, the high-risk HPV infection is pivotal for the progression of cervical cancer. In addition, the genetic changes and epigenetic modifications also play important roles in regulating cervical cancer development [5] [6]. Meanwhile, the primary methods for the treatment of cervical cancer include surgery, radiotherapy and neoadjuvant chemotherapy, which have significantly improved the survival rate of patients [7] [8]. Chemotherapy (CT) is considered as neoadjuvant therapy prior to surgery or radiation, as a sensitizer concomitantly with radiation therapy, or for the treatment of advanced and recurrent cases. CT became a critical component of primary radiation therapy for cervical cancer in 1999 when 5 randomized control trials showed that the addition of cisplatin chemotherapy sensitization to traditional pelvic radiotherapy provided a 30% to 50% improvement in overall survival over radiotherapy alone [9] [10]. Unfortunately, accumulating studies have showed that excessive radio resistance or chemo resistance, repeated relapse as well as tumor metastasis limit the treatment efficacy, and the molecular mechanisms revealing cervical cancer growth are not fully investigated and understood. Therefore, it is urgently necessary to find novel or critical therapeutic target to develop effec-

tive and reliable treatment [11]. In humans, the role of inflammatory cytokines has been investigated in a variety of tumors, including gastric, liver, breast, ovarian, prostate, pancreas, skin, cervix, colon, and hematologic malignancies. Cytokines families studied have included interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and others [12] [13]. In patients, some therapeutic strategies increase tumor cells apoptosis and block their proliferation. In addition, chemotherapy efficacy is depending on the nature and dose of anticancer drugs as well as to tissue sensitivity of the patient. Indirectly, anticancer drugs can influence proportions and functions of immune cells. Evaluations of cell death and lymphocyte activation during chemotherapy would provide evidences for immuno-intervention strategies.

In this study, we evaluated in peripheral blood pro- and anti-inflammatory cytokines levels, their profiles according to treatment issue and relation with prognostic factors in cervical cancer during chemotherapy.

2. Patients and Methods

2.1. Recruitment, Samples Collection and Clinical Management

This study included 36 Senegalese cervical cancer patients (CP) and 42 healthy controls (HC) with no history of malignancy. Patients were recruited from July 2014 to October 2016 in Juliot Curie Institute of Aristide Le Dantec Hospital of Dakar (Senegal). Selected patients were recently diagnosed for cervical cancer without any treatment and managed by the same medical staff with a chemotherapy protocol according to Senegalese recommendations: one cycle every 21 days. Usually three cycles are recommended before undertaking a thorough clinical examination to evaluate therapy response. Each patient followed a treatment protocol depending on individual clinical disease characteristics and general health status. For all the selected patients, Cisplatin was used in combination with 5-fluouracil (5-FU). In terms of doses, cisplastin was administrated 50 - 75 mg/m^2 of body surface every 3 weeks and 5FU was used with to 1000 mg/m^2 every 3 weeks for 3 cycles. HC are women free of cancer or chronic pathologies and recruited at the Immunology Laboratory. Previous cancer treatment, immunosuppression status (case of HIV infection) and death during treatment follow-up were considered as exclusion criteria.

Peripheral blood from all CP and HC was sampled using EDTA vacutainers. For CP, sample collection was based on the treatment protocol. Three samples were collected per patient, corresponding to one before each CT cycle and are designated respectively: Sample 1 (S1), Sample 2 (S2) and Sample 3 (S3). One sample was obtained from each HC women. Samples were immediately centrifuged and sera were stored at −80˚C, prior to cytokines determination.

2.2. Ethics Statement and Procedure

This study was performed at Hospital Aristide Le Dantec in Dakar (Senegal) in

the internal institute dedicated to cancer. Immunological assays were done in the Immunology Unit of the faculty of Medecine of University Cheikh Anta Diop in Dakar. Informed consent was obtained from each participant and/or relatives prior to inclusion, after providing written or verbal information in their native language. The protocol was approved by Institutional Ethics Committee of Cheikh Anta Diop University and registered as the number 0297/2018/CER/UCAD (Dakar, Senegal) and anonymity was maintained.

2.3. Determination of Serum Cytokines Levels

Cytokines levels were measured by SET-GO® ready ELISA kits (Affymetrix eBioscience Inc., San Diego, CA, USA) according to the manufacturer's instructions.

2.4. Statistical Analysis

The data was analyzed with Statview® 5.1. software. To compare cytokines levels between groups, the non-parametric Mann Whitney and Wilcoxon tests were used and correlations were evaluated by using Spearman rank test. Difference was considered as statistically significant for p values < 0.05.

3. Results

3.1. Clinical and Hematological Data of the Study Population

At baseline, hematological characteristics were evaluated for all recruited patients and controls. Data are summarized in Table 1 and comparisons between the two groups highlight significant differences particularly for hemoglobin rates and granulocytes counts. Hemoglobin rates were lower in cancer women group compared to Healthy women (11.54 vs. 13.28; p = 0.024) in addition highest granulocytes counts were found in cancer group (4.92 vs. 1.91; p <0.001) (Table 1).

Table 1. Biological characteristics of the study population.

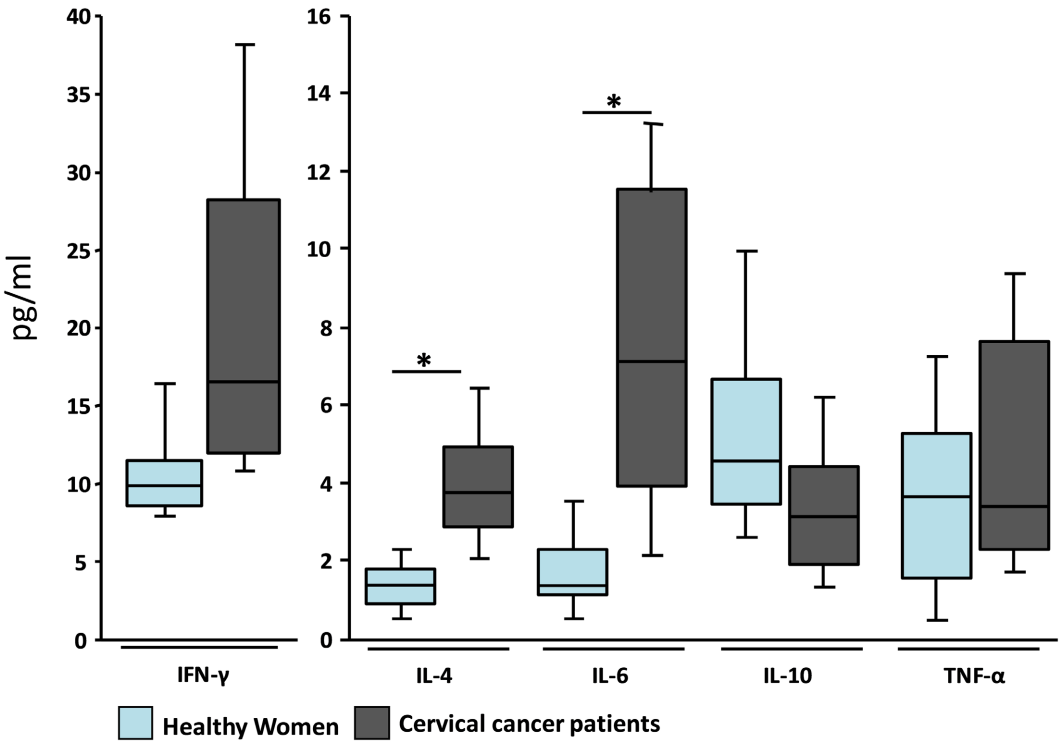
Characteristics	CP (N = 35) Mean (Min-Max)	HC (N = 42) Mean (Min-Max)	p
Age (years)	54.11 (35 - 77)	27.51 (20 - 49)	<0.001
Lymphocytes (10^3/µl)	2.14 (0.86 - 7.95)	2.45 (1.82 - 3.61)	0.112
Monocytes (10^3/µl)	0.80 (0.13 - 4.44)	0.53 (0.31 - 1.45)	0.089
Red blood cells (10^6/µl)	4.97 (2.19 - 14.52)	4.81 (4.17 - 5.50)	0.300
Hemoglobin (g/l)	11.54 (6.81 - 16.53)	13.28 (11.80 - 16.50)	0.024
Hematocrit (%)	36.79 (23.72 - 41.14)	40.25 (36.40 - 48.80)	0.845
Count (10^3/µl)	4.92 (1.85 - 14.52)	1.91 (1.28 - 2.74)	<0.001

Legend: min = minimum, max = maximum, N = number of patients. p = p-value of comparison between CC and HC groups with Mann Whitney rank test.

Clinically, 96% of cervical cancer women presented a squamous cell carcinoma type and adenocarcinoma form was found in 4% of patients. Extension of tumor in the upper third of vagina was observed in group of 24 patients (83%). According to FIGO classification, we found that 37% of cancer women presented the stage IIIa and 21% were on stage IIb. Others observed stages were IIa (15%), IVa (10%), IVb (10%) and IIIb (5%). Menopause was encountered in 72% patients with an average duration of 5 years. In patients group, 7 women had a history of abortions (24%) and average of the gravidity was 7 with extremes ranging from 2 to 14 pregnancies. Regarding the parity, the average was equal to that of the gravidity; it ranged from 1 to 12 children.

3.2. Variations and Relationship between Cytokines Levels in Controls Women and Patients

Before chemotherapy, CP showed higher serum levels of IL-6, IL-4 and IFN-γ compared to HC, with p-value respectively 0,085, 0.002 and 0.002. In patients group, positive correlations were observed about IL-4 levels firstly between S1 and S2 ($r = 0.72$; $p = 0.002$) and secondly between S1 and S3 ($r = 0.73$; $p = 0.019$). Furthermore, between S1 and S3 IFN-γ levels were positively correlated ($r = 0.63$; $p = 0.047$) (Figure 1).



Legend 1. Comparison of cytokines levels between patients (CP) and healthy controls (HC). IFN-γ, IL-4, IL-6, IL-3 and TNF-α are shown as box-whisker plots, representing median with 25th and 75th percentile (boxes) and 10th and 90th percentiles (whiskers). Cytokines levels in cervical cancer patients (CP) in grey are compared to cytokines levels in Healthy controls (HC) in blue. Brackets with asterisk indicate significant differences IL-4 and IL-6 levels (*$p < 0.05$).

Figure 1. Comparison of cytokines levels between patients (CP) and healthy controls (HC).

Levels of pro-inflammatory and anti-inflammatory cytokines were analyzed before and during chemotherapy in CP group. We found lower levels of IL-10 ($p = 0.032$) and TNF-α ($p = 0.016$) in CP compared to HC women. Analyzing levels of TNF-α before chemotherapy and at S1, our results showed a negative correlation ($r = -0.79$; $p = 0.017$), this relationship highlighted a decrease TNF-α concentration during treatment in CP group (Figure 2).

3.3. Profiles of Cytokines Levels According to Chemotherapy's Efficacy

Cytokines profiles were compared according to chemotherapy efficacy between. This comparison shows (Figure 3): i) Good responders patients showed higher serum levels of IL-4 (Figure 3(b)), ii) Partial responders, higher serum levels of TNF-α (Figure 3(c)) and IL-4 (Figure 3(b)), iii) Non-responders patients showed higher serum levels of IL-6 (Figure 3(a)) and IFN-γ (Figure 3(d)) during the follow-up in compared to partial and good responders groups, and lower serum levels of IL-4 (Figure 3(b)) and TNF-α (Figure 3(c)). Significant variations were observed with all cytokines excepted for IL-10 (data no shown).

4. Discussion

In Senegal, cervical cancer is the leading gynecologist-mammary cancer with a percentage of 47.3% of total cancers [14]. There is a well-established cancer center in Dakar that has the capacity to provide surgery, radiotherapy, and chemotherapy. However, the health care system and its patients often do not have the resources to initiate or complete treatment after a cancer diagnosis. Understanding the presentation and outcomes of cervical cancer in patients seeking

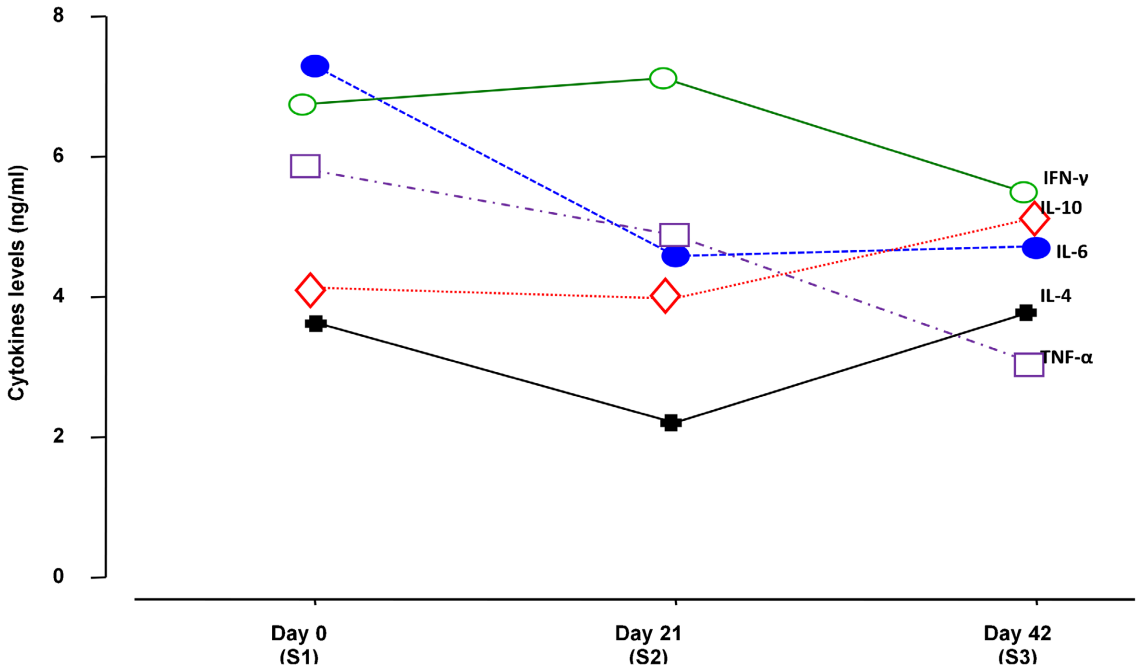
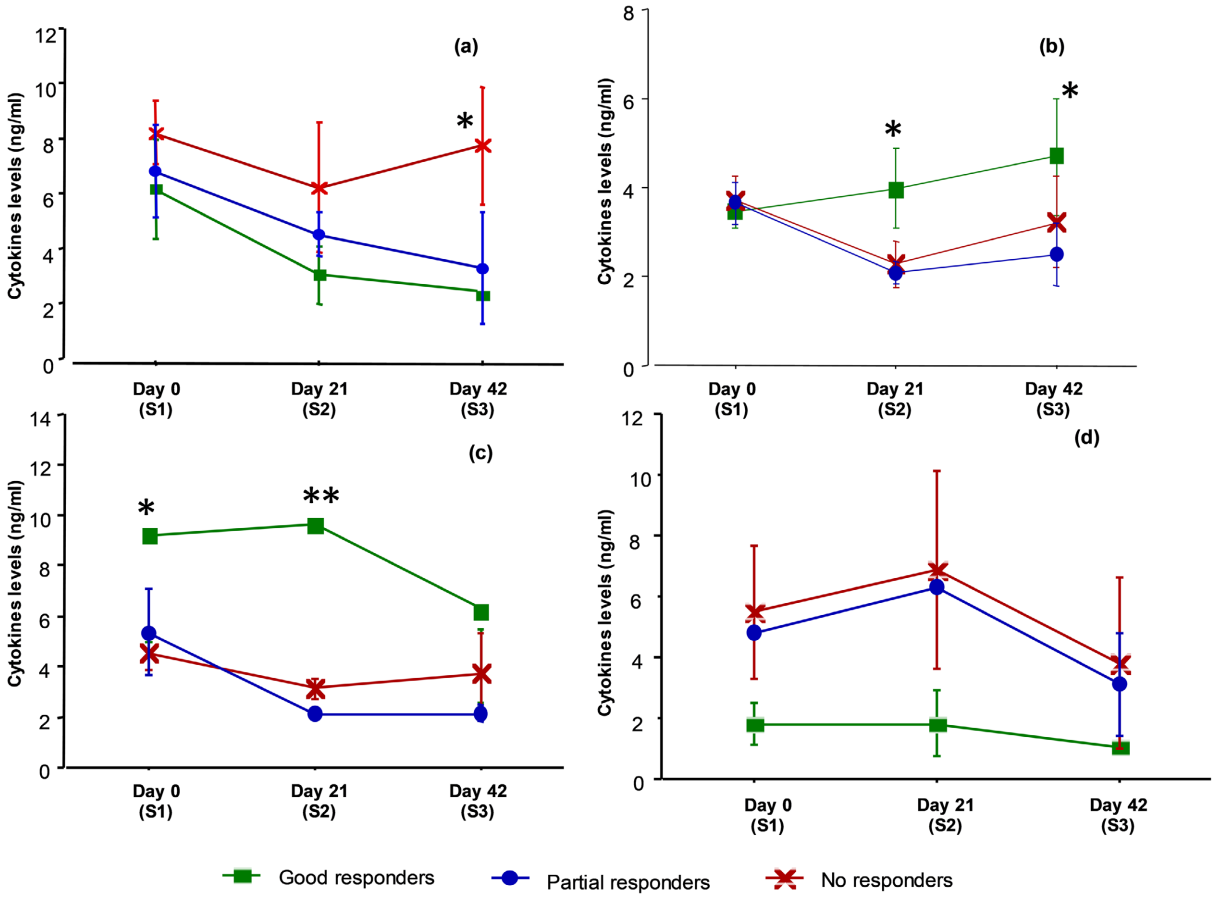


Figure 2. Profiles of cytokines levels in cervical patients during chemotherapy protocol.



Legend 3: Kinetic curves of cytokines levels in individuals with cervical cancer. Shown are the magnitude and kinetic of individual level of cytokines on day 0 (S1), 21 (S2) and 42 (S3) with comparison according to chemotherapy efficacy: good responders (green), Partial responders (blue) and Non responders (red). For each cytokine comparisons were done between the three days of collection. Brackets with asterisk indicate significant differences (*$p < 0.05$ and **$p < 0.01$).

Figure 3. Comparison of cytokines profiles according to chemotherapy efficacy (a) IL-6, (b) IL-4, (c) TNF-α and (d) IFN-γ.

care in these settings can better inform the delivery of care. Cervical cancer remains a real public health problem in Senegal with approximately 1876 new cases of cervical cancer diagnosed each year and no less than 1367 deaths. This is the leading cause of cancer death among women in Senegal [3]. The present study attempts to address this problem by identifying relevant immunological biomarkers. Our main objective was to evaluate the impact of CT on five cytokines levels (IL-4, IL-6, IL-10, TNF-α and IFN-γ) in the peripheral blood of Senegalese women with cervical cancer.

Our results showed that the IL-10 plasma levels in cervical cancer patients are lower than the IL-10 plasma levels healthy people before (significantly) and during treatment. Probably, keratinocytes were related to the destruction of cervical keratinocytes by the virus. Probably, this cytokine that is in part product by keratinocytes is reduce with the invasion of cervical keratinocytes by the virus [15]. Indeed, Keratinocytes are equipped with different pattern recognition receptors (PRRs) but hrHPV has developed ways to dampen their signals resulting

in minimal inflammation and evasion of host immunity for sustained periods of time like described in the study of Rezaul and al on the PRR signaling in non, newly, and persistently hrHPV-infected keratinocytes. They found that active infection with hrHPV hampered the relay of signals downstream of the PRRs to the nucleus, thereby affecting the production of interferon, cytokines and chemokines. This suppression was shown to depend on hrHPV-induced expression of the cellular protein ubiquitin carboxyl-terminal hydrolase L1 in keratinocytes [16].

For the higher serum levels of IL-10 that we observed in our study in non-responders patients this could be explained by one of the key roles of IL-10. Indeed, it acts as an immunosuppressive cytokine by suppressing T-cell proliferation and antigen-presenting cell (APC) functions, and by modulating cytokine and chemokine synthesis. Also, IL-10 expression is elevated during several chronic viral infections, which serves as a viral strategy to down regulate the host immune response and allow viral persistence in the host [17]. The identification of multiple independent association signals located in regulatory regions of IL-10, and the correlation of IL-10 expression with clinical outcome observed in The Cancer Genome Atlas (TCGA) patients, suggest this locus as a putative prognostic marker of melanoma survival [18]. Our study suggests that IL10 as a potential prognostic biomarkers in cervical cancer patients which could contribute to tumor growth and progression. Garbers *et al.* suggested that IL-10 have opposing pro- and anti-inflammatory actions respectively on macrophages, our data are compatible with theirs because levels of IL-10 decrease during treatment [19].

In serum levels of IL-6, our results showed higher levels before and during treatment in patients and in non-responders, this may be due to cervical carcinoma lines secreting more IL6 than normal or immortalized cervical lines [20] [21]. Consistent with our data, increased IL-6 mRNA expression was found in cervical tumors compared to dysplastic lesions or normal cervixes [22]. Moreover, proliferative effects of IL-6 were previously reported during tumor lines culture. Indeed, the mitogenic effect of certain sera can mask the growth factor effect of IL-6, and certain sera induce the secretion of endogenous IL-6 in vitro. Interestingly, the Th2 cytokine IL-6 is constitutively released by keratinocytes harboring HPV-16 and expressed at higher levels in invasive cervical carcinoma. By different approaches, it therefore appears that IL-6 is a cervical tumor growth factor in vitro and in vivo. Other properties of IL-6, such as its anti-apoptotic action or its properties that inhibit inflammatory reactions, may also explain this protumoral activity of IL-6 [23].

Our study showed although higher serum levels of IFN-γ before (significantly) and during treatment in patients and in non-responders. Some studies have shown that IFN-γ also plays a role in adaptive resistance [24]. Indeed, it induces the loss of antigen expression and the induction of ligand decreasing the action of the immune system [25]. In addition to their anti-tumor properties, type I and

type II IFNs have been shown to be involved in pro-tumor effects. Mouse mammary tumor cells exposed to low doses of IFN-γ are not killed by NK cells or T cells. Recently, transplant experiments carried out in syngeneic, immunocompetent mice have shown that type I IFNs are not only produced by cells of the immune system, but also by tumor cells. In fact, the tumors were recovered after chemotherapy and the cells were sorted so as to separate the immune cells from the tumor cells. Then, a transcriptome was performed on the tumor cells and the results were confirmed by quantitative PCR. These experiments revealed that the overexpression of ISG and IFNβ was found in the tumor cells themselves thus showing that the cells of the immune system are not the only ones to contribute to the IFN-γ production [26].

As the IL-6 levels, higher serum levels of IL-4 before (significantly) and during treatment, and higher with good-responders patients is commonly observed. Some studies have demonstrated the important anti-tumor role of IL-4 in vivo. Indeed, lineages murine plasmacytomas lose their tumorigenicity following the introduction of an active IL-4 gene [27]. The antitumor effect would be indirect and would be achieved by the recruitment and stimulation of macrophages and eosinophilic granulocytes, these results associated with the immune-stimulatory properties of IL-4 certainly encourage the use of this cytokine in cancer patients.

Our results although showed that the TNF-α plasma levels in cervical cancer patients are lower than the TNF-α plasma levels healthy people before (significantly) and during treatment. It may be explained by the fact that TNF-α levels are raised in multiple cancer types, are reduced by chemotherapy and the reduction is associated with patient outcomes [28]. These results are in line with another work using mice showing that despite its potential to activate cell death processes, physiological intra-tumor TNF levels are likely insufficient to induce cancer regression in mice as well as in patients [29]. Finding ways to increase production of this cytokine can potentiate the efficacy of immunotherapy, yet selective targeting of TNF in the tumor mass as well as management of the toxicity associated with such approaches remains a concern.

5. Conclusions

In summary, our results highlight the role of circulating cytokines of inflammation IL-6, IL-10 and IFN-γ as the potential prognostic biomarkers in cervical cancer patients, which could contribute to tumor growth and progression. These results suggest that IL-4 and TNF-α might represent candidate CC biomarkers. For cervical cancer patients, there is the possibility to access tumor tissue throughout a patient's treatment, which presents the unique opportunity for adapting treatment based on changes in biomarkers. Initial studies show that these cytokines could also constitute new clinical prognostic markers for these pathologies.

The challenge for the next few years will be to demonstrate that original the-

rapeutic approaches can result from this work.

Consent for Publication

Written informed consent was obtained from all the participants.

Ethics Approval and Consent to Participate

This research was approved by Institutional Ethics Committee of Cheikh Anta Diop University (Dakar, Senegal), Reference number: 0196/2016/CER/UCAD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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