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Original Article

Circulating interleukin-18 (IL-18) is a predictor of response to gemcitabine based chemotherapy in patients with pancreatic adenocarcinoma

Çiğdem Usul Afsar [a, *], Mehmet Karabulut [b], Senem Karabulut [c], Halil Alis [b], Murat Gonenc [b], Nergiz Dagoglu [d], Murat Serilmez [e], Faruk Tas [c]

[a] Clinic of Medical Oncology, Istanbul Education and Research Hospital, Istanbul, Turkey
[b] Clinic of General Surgery, Istanbul Bakırköy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey
[c] Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey
[d] Department of Radiation Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey
[e] Department of Basic Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey

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ABSTRACT

Background: This study was conducted to investigate the serum levels of interleukin-18 (IL-18) in patients with pancreatic adenocarcinoma (PA) and the relationship with tumor progression and known prognostic parameters.

Methods: Thirty-three patients with PA were studied. Serum samples were obtained on first admission before any treatment. Serum IL-18 levels were analyzed using enzyme-linked immunosorbent assay (ELISA). Age- and sex-matched 30 healthy controls were included in the analysis.

Results: The median age at diagnosis was 59 years, range 32–84 years; 20 (61%) patients were men and the remaining were women. The median follow-up time was 26.0 weeks (range: 1.0–184.0 weeks). The median overall survival of the whole group was 41.3 ± 8.3 weeks [95% confidence interval (CI) = 25–58 weeks]. The baseline serum IL-18 levels were significantly higher in patients with PA than in the control group ($p < 0.001$). Serum IL-18 levels were significantly higher in the patients with high erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH) ($p = 0.01$ and $p = 0.05$). Moreover, the chemotherapy-(CTx) unresponsive patients had higher serum IL-18 levels compared to CTx-responsive ($p = 0.04$) subjects. Conversely, serum IL-18 concentration was found to have no prognostic role on survival ($p = 0.45$).

Conclusion: Serum levels of IL-18 can be a good diagnostic and predictive marker; especially for predicting the response to gemcitabine based CTx in patients with PA but it has no prognostic role.

1. Background

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in the United States among both men and women. The majority of these tumors (85%) are adenocarcinomas arising from the ductal epithelium [1,2]. PC has an extremely high mortality rate due to its aggressive metastatic nature. Factors derived from both genetic and surrounding microenvironment may contribute to this aggressive nature [3]. In PC, severe desmoplastic response is usually observed around the primary tumor [4]. These stromal cells secrete cytokines, growth factors, and angiogenic factors to promote tumor growth [5] and metastasis [6].

Interleukin-18 (IL-18), a member of the IL-1 family, is synthesized as an inactive preform, and then converted to a bioactive form [7–10]. In addition to multiple biological activities by its capacity of stimulating immunity, it also exerts antitumor effects that are mediated by the enhancement of NK (natural killer) cell activity, reduction of tumorigenesis, induction of apoptosis, and inhibition

* Corresponding author. Clinic of Medical Oncology, Istanbul Education and Research Hospital, Kasap Ilyas Mah. Org. Abdurrahman Nafiz Gürman Cd., PK: 34098, Istanbul, Turkey. Fax: +90 2124596230.
E-mail address: cigdemusul@yahoo.com (Ç. Usul Afsar).

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of angiogenesis in tumor cells. Recent data suggest that an inappropriate production of IL-18 contributes to the pathogenesis of malignancies and may influence the clinical outcome of patients [7–10].

For PC; elevated serum levels of free IL-18 are correlated with poor survival [11]. Furthermore, in another study, it was found that adjuvant polychemotherapy including 5-FU, significantly increased serum levels of mature, bioactive IL-18 in pancreatic carcinoma patients [12]. This showed that chemotherapeutic agents may modulate local anti-tumor cell-mediated immune responses. There is a dendritic cell vaccine modified with tumor lysate and the IL-18 gene which is shown to induce a specific and effective immune response against pancreatic carcinoma cells in literature but it was a mice model and was not verified with other studies up to now [13].

In this study, our aim was to investigate the serum levels of IL-18 in patients with PA and the relationship with tumor progression and known prognostic parameters, especially in predicting a response to gemcitabine based CTx. To our knowledge, this is the first study which shows that IL-18 is a predictor of a response with gemcitabine based CTx.

2. Methods

2.1. Patients' characteristics

The recorded data of 33 patients with histologically confirmed diagnosis of PA, were treated and followed up in our clinic. Chemotherapy (CTx) was given to the majority of the patients with metastatic disease (n = 20, 61%). Drug schemes were

Table 1
Characteristics of the patients and disease.

Variables	n
No. of patients	33
Age (years)	
Median (range)	59 (32–84)
Gender	
Male/Female	20/13
Performance status (PS)[a]	
0/1/2/3	4/19/5/4
Weight loss[a]	
Yes/no	26/4
Jaundice[a]	
Yes/no	9/22
Surgery type[b]	
Whipple surgery/palliative surgery	5/3
Pathologic tumor (pT) size[a]	
<Small (<40 mm)/≥ large (≥40 mm)	14/14
Site of lesion	
Head/corpus-tail	21/10
Response to chemotherapy (CTx)	
Yes (PR + SD)/no (PD)	9/11
Metastasis	
Yes/no	23/10

[a] Patients with unknown data concerning the variables are not included in the analysis.
[b] In 10 patients with non-metastatic.

Table 2
The laboratory parameters of the patients.

Variables	n
Erythrocyte sedimentation rate (ESH)	
Normal (<40/h)/high (>40/h)	11/12
White blood cell count (WBC)[a]	
Normal (<10.000/mm^3)/high (>10.000/mm^3)	22/9
Hemoglobin (Hb)[a]	
Low (<12 g/dl)/normal (>12 g/dl)	12/19
Platelet count (PLT)[a]	
Low (<150.000/mm^3)/normal (>150.000/mm^3)	5/26
Lactate dehydrogenase (LDH)[a]	
Normal (<450 IU/l)/high (>450 IU/l)	21/8
Albumin[a]	
Low (<4 g/dl)/normal (>4 g/dl)	10/17
Carcinoembryonic antigen (CEA)[a]	
Normal (<5 ng/ml)//high (>5 ng/ml)	19/10
Carbohydrate antigen (CA 19.9)[a]	
Normal (<38 U/ml)/high (>38 U/ml)	7/22

[a] Patients with unknown data concerning the variables are not included in the analysis.

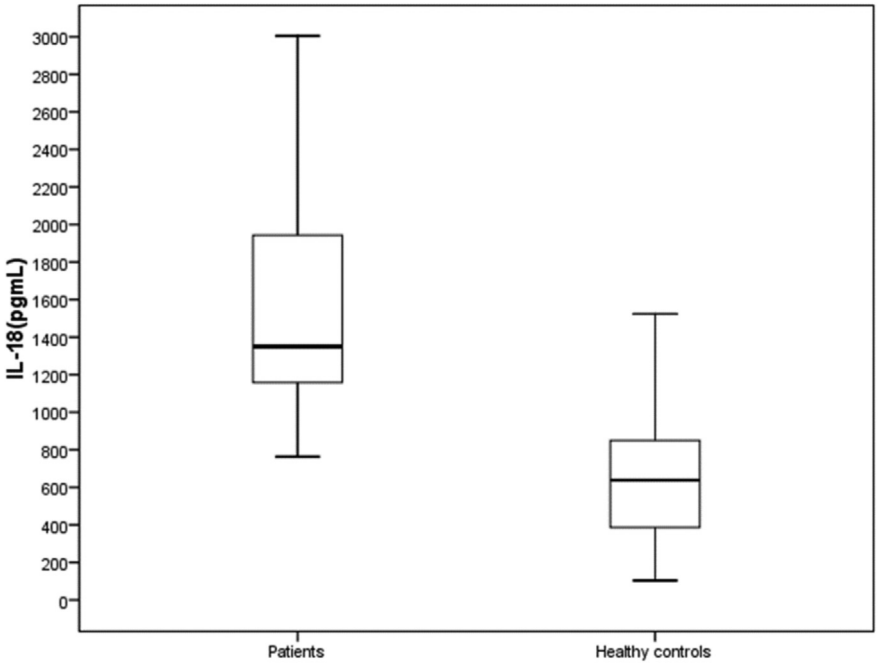

Fig. 1. The values of serum IL-18 assays in pancreatic cancer patients and controls ($p < 0.001$).