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REVIEW

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Cytokine patterns in cancer patients: A review of the correlation between interleukin 6 and prognosis

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ABSTRACT

Objective: In tumor patients, IL-6 appears to be one component of a consistent cancer-associated cytokine network resulting in both a systemic immune stimulation and a microenvironment of cancer-induced immune suppression that ultimately protects the cancer cells. IL-6 has been associated with prognosis in cancer patients, but so far a systemical analysis has not been carried out. **Methods**: The present meta-analysis studies the relation between IL-6 serum levels and the prognosis of cancer patients in the available clinical literature of 100 articles published between 1993 and 2013 comprising 11,583 patients. **Results**: The IL-6 serum level was described as significantly correlating with survival in 82/101 series comprising 85.6% of patients (9917/11,583) with 23 different cancer types. A total of 64 studies dichotomized patient cohorts according to various cut-off IL-6 serum levels: in 59/64 of these series corresponding to 94.5% of the reported patients (7694/8142) significant correlations between IL-6 serum level and survival were seen. The median survival of cancer patients had been determined above various cut-off levels of serum IL-6 in 24 dichotomized studies (26 cohorts). There was a highly significant inverse correlation between median survival of the cohorts with IL-6 serum level above cut-off (1272 patients) and their corresponding IL-6 cut-off values (Spearman R -0,48 p= < 0.001) following a linear regression when both parameters were log-transformed ($p < 0.001$). A significant correlation between increasing serum IL-6 and tumor stage or metastases was described in 39/44 studies and 91% of published patients (4221/4636) where clinical parameters had been specified. **Conclusions**: Closely associated with the patient's clinical condition and independent of the cancer histology, the increased IL-6 serum level uniformly appears to correlate with survival as paraneoplastic condition in later cancer stages independent of the cancer type. Modifications of this paraneoplastic immune reaction may offer new therapeutic options in cancer.

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Introduction

Independent of the original tumor pathology, patients with advanced stage cancer appear to experience a simultaneous immunostimulation and immunosuppression with increased concentrations of cytokines including MIF, TNF-a, IL-18, IL-8, IL-6, TGF-β, and IL-10.(Reviewed in.[1]) The result is a local inflammatory environment that appears to be a consistent component of malignant tumors.[2,3] The simultaneous cancer-induced activation of the immunosuppressive cytokines IL-10 and TGF-β, however, results in a dysfunction of antigen-presenting cells (APCs) and the conversion of conventional T cells into Tregs in the tumor microenvironment.[4] The functional result is an impaired antigen detection and dysfunction of effector cells of both the innate and adaptive immune systems despite a general environment of immune stimulation. The described cytokine pattern interferes with immunological effector mechanisms and could prevent both physiological tumor immunodetection and tumor destruction. This dysfunctional immunostimulation could be one of the reasons why macrophages are locally attracted but inactivated and even incorporated into neoplasms: tumor-associated macrophages (TAM) with a predominantly immunosppressive (IL-12^{low}/IL-10^{high}; M2) phenotype represent the major inflammatory component of the stroma of many tumors.[5]

This consistent paraneoplastic cytokine pattern appears to be independent of the initial tumor histology and a phenomenon of late-stage cancer patients.[1] The cytokine IL-6 is an essential component in this functional circuit: IL-6 and its soluble receptor (sIL-6Ra) appear to have a key role in the transition from an acute toward a sustained or even chronic inflammation by decreasing neutrophil and favoring mononuclear-cell accumulations.[6-8] IL-6 induces the final maturation of B cells into antibody producing cells.[9,10] and, together with TGF-b it induces a key regulatory signal in the generation of Th17 cells,[11-15] while concomitantly blocking the differentiation of CD4$^+$ cells into regulatory T cells.[15-20] IL-6 stimulates proliferation and migration of circulating endothelial progenitor cells.[20,21] and has a pivotal physiological role in wound healing, possibly by regulating leukocyte infiltration and collagen deposition.[22] Cytokine interactions comprise sophisticated interdependent positive and negative feedback mechanisms that provide homeostasis and control. Cytokines interact in

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functional circuits with impact on both agonistic and compensatory antagonistic effects. For example, IL-6 can regulate the production of IL-10 from carcinoma cells,[23,24] which in turn can have a downregulating effect on IL-6.[25]

Several clinical series have independently reported a correlation between IL-6 and patient prognosis in various cancer types. In general, clinical research is focused on analysis of specific tumors types and the search for common traits in different clinical cancer types is almost obsolete with respect to cancer heterogeneity. Despite multiple independent recordings, the correlation between IL-6 and prognosis has so far not been comprehensively cross-referenced or systematically analyzed and has thus been widely un-noticed. So far, there is no oncological concept for the role of IL-6 in clinical cancer.

The current review analyses the available clinical literature of the recent two decades and identified studies that describe the prognostic and clinical impact of IL-6 in cancer patients. An attempt is made to quantify the cumulative results in a meta-analysis.

Materials and methods

Article selection and analysis

A systematic search of IL-6 in cancer patients was conducted using the PubMed database. The search was filtered according to 'prognostic impact of IL-6 in cancer patients' with the publication interval 1993–2013 (the search algorithm is added as an attachment). Only human clinical studies were included. No limits were set on cancer type or duration of follow-up. The studies were determined eligible for inclusion if they were original research studies that reported on IL-6 in cancer patients, and reviews were excluded. Corresponding authors were contacted to clarify missing data. The inclusion of duplicated or overlapping data was avoided by comparison of authors and institutions. A thorough review of all referenced sources was performed. Among 100 articles, 101 published series were identified in which the serum level of IL-6 was analyzed with respect to survival, with 92 articles being identified via direct searches and 8 articles via cross-references. (One study differentiated between the outcome of 159 patients in a gemcitabine/placebo group and 169 patients in the gemcitabine/bevacizumab group with different results with respect to IL-6, and these were considered as two separate series.[26]) Correlations between IL-6 serum level and overall survival or tumor stage were the primary and secondary outcomes of interest.

Quantitative analysis of survival of cancer patients at specific cut-off values for serum IL-6

Among the selected series, those studies were identified that had applied various cut-off values for serum IL-6 levels and had reported the median survival of the cancer patients with IL-6 serum levels above the cut-off. In one study, the median survival was not mentioned in the text and was communicated personally.[27] A total of 24 series, each comprising more than 50 patients were analyzed quantitatively using the Statistica 12 software ([28,29] excluded due to small sample size). Two studies determined survival using two different cut-off values for serum IL-6, resulting in a total of 26 pairs of variables. The median survival of

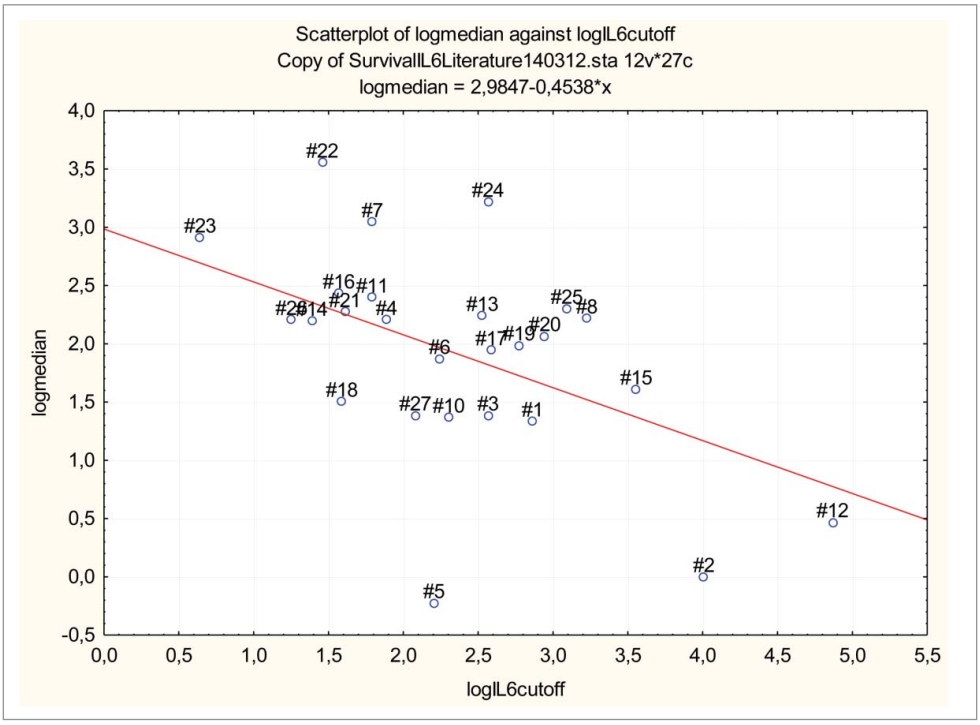

Figure 1. Median survival of 1272 cancer patients with IL-6 serum levels above various chosen cut-off values in 24 dichotomized studies (26 cohorts). Both *x* and *y* parameters have been have log-transformed in the graph. Sample size was used to weigh the studies. The median survival at chosen cut-off points was inversely correlated to the minimum IL-6 serum level at this cut-off, both when sample size was used to weigh the studies ($p < 0.001$) and also when the cohorts were not weighted ($p < 0.005$). Numbers indicate series as listed in Table 2.

cohorts of patients with serum IL-6 above the reported cut-off level (in 1272 patients) was plotted against the applied cut-off level of serum IL-6 of each series (Fig. 1). The non-parametric Spearman's Rank order Correlation was applied in a non-weighted and weighted mode. Both parameters were log-transformed and a linear regression model was applied for the determination of correlations. In one version, the result was weighted according to the number of patients in each study and in the second version results were not weighted. Fisher Test was applied to test the regression model for significance.

Results

IL-6 serum level in cancer and controls

The median serum level of IL-6 in cancer patients was documented in 72 studies. The median of the reported median IL-6 serum level in cancer patients was 6.95 pg/mL (range: 0.23–78.5 pg/mL). The median of the reported median IL-6 serum level in control cohorts (available in 40 series) was 1.31 pg/mL (range 0–37 pg/mL). In 57 studies, serum IL-6 was compared against a healthy control group: IL-6 was increased in cancer patients in 53/57 studies comprising 94.02% of patients (5985/6366 patients).

Serum IL-6 and survival

The serum level of IL-6 was studied with regard to survival in 101 series in 100 articles encompassing 11,583 patients. Overall survival was reported in 100 series and failure-free survival was reported in one article.[30] The serum level of IL-6 was described as significantly associated with survival in 82/101 series (100 articles) in 9917/11,583 patients (85.6%) in 23 different cancer types (Table 1). Seven series analyzed multiple cancer types comprising patients with hepatobiliary system cancer, gastric cancer, head-and-neck cancer, melanoma, liver cancer, lymphomas, squamous cell cancers, sarcoma, leukemias, renal cancers, unknown adenocarcinoma, ovarial cancer, colorectal cancer, lung cancer, breast cancer and cervical cancer.[27,31-36] In all of these seven non-selected cohorts of cancer patients,[27,31-36] IL-6 was significantly associated with survival. In 32/57 studies comprising 4441/7362 patients, multivariate analyses had been applied revealing a prognostic impact of serum IL-6, while in 25/57 studies comprising 2921 patients the correlation was only apparent using univariate analysis. The serum level of IL- 6 had no significant prognostic relevance in one series of glioblastoma.[37] and in both series of patients with acute myelogenous leukemia.[38,39]

Dichotomized studies

Patients were dichotomized according to various IL-6 serum cut-off levels in 64 studies comprising 8142 patients. The overall median of the reported median cut-offs of serum IL-6 was 10 pg/mL (range: 1.9–130 pg/mL) in cancer patients. Among the dichotomized studies a significant correlation between IL-6 serum level and survival was found in 59/64 series (92.2% of studies) comprising 94.5% (7694/8142) of the reported patients.

Quantitative analysis of survival of cancer patients at specific cut-off values for serum IL-6

The median survival of cancer patients had been determined below and above various cut-off levels of serum IL-6 in 24 studies each containing more than 50 patients and thus comprising a total of 2830 cancer patients. In a total of 1272 patients in 26 cohorts, the median survival was reported for patients in whom

Table 1. Summary of clinical series with cancer patients that reported the serum level of IL-6 and its potential association with survival.

Cancer types where IL-6 was shown to have a significant impact on survival		Series *with* significant impact of serum IL-6 on overall survival (reference number)	Series *without* significant impact of serumIL-6 on overall survival (reference number)
1. Pancreatic cancer	In 6 out of 8 series	26,86,98-101	26,56
2. Breast cancer	In 6 out of 7 series	102-107	108
3. Colorectal cancer	In 5 out of 10 series	109-113	59,60,62,114,115
4. Carcinoma of the esophagus	In 1 out of 1 series	116	
5. Laryngeal squamous cell cancer	In 1 out of 1 series	117	
6. Ovarian cancer	In 3 out of 4 series	42,43,118	58
7. Non-small-cell lung cancer and lung cancer	In 10 out of 12 series	119-128	57,129
8. Small cell lung cancer	In 1 out of 1 series	130	
9. Gastric cancer	In 6 out of 7 series	84,131-134	63
and advanced gastrointestinal cancer	In 1 out of 1 series	135	
10. Biliary tract cancer (advanced)	In 1 out of 1 series	136	
11. Renal cancer	In 7 out of 8 series	28,137-142	65
12. Head and neck cancer	In 1 out of 1 series	143	
13. Prostate cancer	In 3 out of 3 series	144-146	
14. Bladder cancer	In 1 out of 1 series	147	
15. Bone sarcoma	In 1 out of 1 series	148	
16. Soft tissue sarcoma	In 1 out of 1 series	149	
17. Malignant melanoma	In 5 out of 6 series	150-154	66
18. Classical Hodgkin's lymphoma	In 1 out of 1 series	155	
19 Diffuse large cell lymphoma	In 2 out of 2 series	156,157	
20. Non-Hodgkin lymphoma	In 8 out of 10 series*	29,30,45,158-162	61,64
21. T-cell leukemia/lymphoma	In 2 out of 2 series	163,164	
22. Chronic lymphocytic leukemia	In 1 out of 1 series	89	
23. Neuroblastoma	In 1 out of 1 series	165	

* Fayad [30]: failure-free survival.

the IL-6 serum level was higher than the chosen cut-off value (Table 2). The cut-off value hence represented the minimum serum IL-6 level of the cohort. When sample size was used to weigh the studies, the median survival at the chosen cut-off points was inversely correlated to the minimum IL-6 serum level at this cut-off and this inverse correlation between median survival and chosen IL-6 serum level was highly significant (Spearman R -0.48, $p = < 0.001$). The correlation was similarly significant, when the median survival above serum IL-6 cut-off was determined without respect to sample size (Spearman R -0,402 $p = < 0.04$). The median survival of all 26 cohorts was plotted against this minimum IL-6 serum level and both parameters were log-transformed. On linear regression analysis, the median survival at the chosen cut-off value was inversely correlated to the corresponding minimum IL-6 serum level, both when sample size was used to weigh the studies ($p < 0.001$) (Fig. 1) and also when the cohorts were not weighted ($p < 0.005$).

Serum IL-6 and tumor stage or metastases

Clinical parameters had been recorded and correlated with IL-6 serum levels in 44 series. A significant correlation between increasing serum IL-6 and increasing tumor stage or metastases was found in 39/44 studies comprising 91.04% (4221/4636) of the studied patients.

Discussion

Cancer induces both directly tumor-related symptoms and a systemic paraneoplastic condition that is not directly associated with the neoplasm. Besides highly heterogeneous aspects of various tumor types, there are common clinical denominators in patients with late-stages cancer. Corresponding to these clinical symptoms, there is evidence for a common paraneoplastic phenomenon in patients with advanced cancer that is expressed through a uniform cytokine pattern that appears to be independent of the cancer type.[1] The resulting condition can be summarized as cancer-associated dysfunctional immunostimulation, where the inflammatory microenvironment has a significant impact in the development of cancer.[2] IL-6 is an essential component in the cytokine cascade that is involved in the generation and regulation of inflammation. It has been previously discussed that IL-6 could be associated with survival in individual cancer patients, but the available clinical data have so far been fragmented and inconclusive. The present comprehensive literature review studied IL-6 with regard to survival in in 100 articles comprising a total of 11,583 cancer patients. The goal was to describe the clinical impact of IL-6 in cancer patients and to integrate the existing experimental immunological data into the clinical context in a translational analysis.

The fact that a majority of studies (39/44) reported a correlation between increasing IL-6 and increasing tumor stage or metastases demonstrates that the increase of the IL-6 serum level appears to be a late-stage phenomenon in cancer patients.

The current review demonstrates that the serum level of IL-6 was increased in the vast majority of clinical cancer studies with a significant correlation between serum IL-6 and survival being documented in 86% of reported patients in 23 different cancer types (Table 1). Hence, the increase of serum IL-6 appears to

Table 2. In 24 dichotomized studies (26 cohorts) comprising 1272 patients, the median survival was reported for patients in whom the IL-6 serum level was higher than the chosen cut-off value. References, primary cancer type, number of patients, cut-off for IL-6 serum level (pg/mL) and median survival are given in the table.

References	Corresponding number in Fig. 1	Tumor type	Number of patients	IL-6 cut-off (in pg/mL)	Median survival at IL-6 above chosen cut-off
Nixon et al.[26]	1	Advanced pancreatic cancer	84	17.5	3.8
Bachelot et al.[105]	2	Metastatic breast cancer	8	55	1
Bachelot et al.[105]	3	Metastatic breast cancer	23	13	4
Salgado et al.[106]	4	Metastatic breast cancer	47	6.6	9.08
Suh et al.[31]	5	Various advanced cancer	49	9.06	0.8
Di Nisio et al.[35]	6	Various advanced cancer	70	9.4	6.5
Scambia et al.[118]	7	Ovarian cancer	57	6	21
Chang et al.[120]	8	Advanced NSCLC	81	25.16	9.2
Songür et al.[125]	9	Advanced NSCLC	48	10	3.93
Wójcik et al.[130]	10	Small cell lung cancer	35	6	11
Martin et al.[127]	11	Lung cancer	16	130	1.6
De Vita et al.[135]	12	Advanced gastrointestinal ca.	34	12.53	9.4
Guida et al.[139]	13	Metastatic renal cell carcinoma	33	4	9
Negrier et al.[140]	14	Metastatic renal cell carcinoma	34	35	5
George et al.[144]	15	Hormone-refractory prostate cancer	95	4.8	11
George et al.[144]	16	Hormone-refractory prostate cancer	46	13.31	7
Hoejberg et al.[150]	17	Metastatic melanoma	44	4.9	4.5
Guida et al.[151]	18	Metastatic melanoma	25	16	7.3
Mouawad et al.[152]	19	Metastatic melanoma	35	19	7.9
Soubrane et al.[154]	20	Metastatic melanoma	76	5	9.7
Preti et al.[156]	21	Diffuse large-cell lymphoma	62	4.3	35
Seymour et al.[157]	22	Diffuse large-cell lymphoma	44	1.9	18.4
Pedersen et al.[45]	23	Aggressive non-Hodgkin's lymphoma	32	13	25
Kurzrock et al.[162]	24	Hodgkin's disease and non-Hodgkin's lymphoma	20	22	10
Yamamura et al.[164]	25	Adult T-cell leukemia/lymphoma	44	3.5	9.08
Trédan et al.[27] (and Trédan personal communication)	26	Various cancer types: breast ca. (45%), lung ca. (15%), ovarial ca. (11%), other ca. (29%)	130	8	4

reflect a systemic phenomenon that is independent of the initial tumor histology.

The median survival of cancer patients had been determined below and above various cut-off levels of serum IL-6 in 24 studies and 26 cohorts with the cut-off value hence representing the minimum serum IL-6 level of a specific published cohort. The analysis showed a highly significant inverse correlation between median survival of the cohorts and their corresponding IL-6 cut-off values (Spearman R -0.48, $p = < 0.001$) following a linear regression when both parameters were log-transformed ($p < 0.001$) (Fig. 1). The result is surprising since each variable represents the median survival of a specific patient cohort with different cancer types, where an independent predictor of survival would be counterintuitive. This form of graphic representation and resulting analysis was chosen to allow an initial meta-analysis of the potential impact of IL-6 in a larger number of published patients.

The finding that IL-6 correlates with overall survival in the majority of studies in 23 different cancer types supports the concept of a uniform and paraneoplastic immune reaction in late-stage cancer patients. Although this finding clearly requires confirmation in specific prospective studies, the significant correlation between the serum IL-6 level and the survival in late-stage cancer could provide a novel and simple way of monitoring the systemic involvement of the immune system in cancer patients and the resulting clinical deterioration.

An essential question is if the cancer-associated immunological involvement and consistent cytokine pattern in late-stage patients.[1] is instrumental in the clinical deterioration of cancer patients or if the increasing dysfunction of the immune system is a mere neoplastic epiphenomenon.

In concordance with the concept of IL-6 as a prognostic indicator, several studies documented reduced IL-6 serum levels in cancer patients who had been successfully treated through either chemotherapy or surgery. In lung cancer patients, serum IL-6 levels on the first post-operative day were significant independent predictors for early recurrence,[40] and others showed that positive response to chemotherapy correlated with lower IL-6 levels.[41] In ovarian cancer patients, the serum level of IL-6 (and of CA-125, IL-7, IL-8, IL-10) decreased following chemotherapy[42] or surgery.[43,44] and early changes in serum IL-6 levels predicted the clinical outcome in patients with non-Hodgkin's lymphoma, where IL-6 levels decreased significantly in responding patients.[45]

It is interesting that a similar relation between IL-6 serum level and prognosis has also been described in patients with septic shock, where elevated IL-6 plasma concentrations have been defined as an important biochemical indicator for early prediction of a lethal outcome,[46-53] even in large prospective randomized series.[54]

Inflammation appears to be a hallmark of cancer. Despite being initially postulated by Virchow more than a century ago, for a long time the correlation between inflammation and cancer has received very little attention. IL-6 is an essential component of the systemic inflammatory immune reaction. The widespread histology-independent presence of IL-6 in late-stage cancer patients could indicate that the immune response mechanism is initiated by the tumor, but ultimately results in a paraneoplastic systemic reaction that is independent of the cancer form.

The widespread and uniform impact of IL-6 on clinical parameters including overall prognosis of cancer patients is counterintuitive with regard to the diversity of cancer types. It could be argued that a potential uniform immune reaction pattern in cancer would not reflect the differences in malignant phenotypes and variability in biological neoplastic behaviors. Conversely, the process of immune-editing is an increasingly established principle stating that a neoplasm is formed as the result of an immunological selection process ultimately producing tumor cells which are resistant to potential immune attacks.[55] In this scenario, the malignant cellular selection process is uniformly shaped by the homogenous physiological conditions of the human immune response. These consistent conditions could explain a uniform paraneoplastic cytokine pattern that is associated with cancer.

Exceptions

A number of publications did not determine a correlation between overall survival and IL-6. Several of these studies can be categorized: some reported atypically high serum IL-6 levels in control cohorts or patients[56,57].(20.41 pg/ml [56] 37 pg/mL[57]) whereas the median level of all the published medians of IL-6 in control groups and cancer patients were 1.31 pg/mL (40 series: range 0–37 pg/mL) and 6.95 pg/mL (72 series: range 0.23–78.5 pg/mL), respectively. Other series without prognostic impact of IL-6 had not determined a difference between IL-6 in patients and controls,[57-59] which is an unusual finding since median IL-6 serum level in cancer patients was otherwise increased in 53/57 studies comprising 94.02% (5985/6366) of patients. In some studies of patients in a very early stage of cancer[60] or with a very long survival time (median survival 9 y)[61] IL-6 did not have an impact on survival. For example, in a study of indolent lymphoma, where IL-6 was unrelated to prognosis, only very few patients had died after the observation period, thus precluding conclusions.[30] In two studies with colorectal and gastric cancer patients, serum IL-6 was not predictive for survival but nevertheless the levels of IL-6 increased with tumor stage, and concentrations of IL-6 in the patients who died from cancer were significantly higher than in those who survived.[62,63] Five studies did not show a correlation between survival and serum IL-6 levels without falling under the described categories.[26,37,64-66] One of these studies analyzed patients with glioblastoma,[37] where the local tumor growth in the brain could become the determining factor for survival rather than the systemic immune response.

Functions of IL-6

A physiological immune reaction is based on multiple positive and negative feedback mechanisms involving multiple cell types that require a coordinated choreography for their efficacy and homeostasis. Cytokines have important roles in the coordination of events. The following simplified sequence of events has been proposed by Kaplanski and colleagues.[6] and clarifies some aspects of IL-6 in the interactive process of the immune reaction: during acute inflammation macrophages respond to inflammatory stimuli by immediate production of TNF-α, IL-1 and chemokines. TNF-a induces IL-8, which induces early

neutrophil recruitment into the inflammatory site.[6,67] Activation of neutrophils by IL-8 promotes cleavage and shedding of IL-6R from the surface of neutrophils.[6,68] thus promoting 'trans-signaling' of IL-6 to cells that do not express the IL-6 receptor but that express gp130.[69-72] In addition, TNF-α induces IL-6 gene expression in monocytes and macrophages (Reviewed in [20]) and IL-6 expression triggers the hepatic acute phase reaction.[20,73] IL-6 supports the inflammation since it provides a signal in the development of Th17 cells while blocking the differentiation of $CD4^+$ cells into Treg cells.[11] Th17 cells are inducers of tissue inflammation and Treg cells have immunosuppressive functions.[74]

Initially neutrophils infiltrate the tissue during acute inflammation but are later replaced by a more sustained population of mononuclear cells. It has been said that IL-6 "orchestrates this temporal switch" during inflammation.[7] This step appears to be controlled by IL-6 and its soluble receptor (sIL-6R),[7] which activate endothelial cells to produce monocyte chemotactic protein-1, thus stimulating monocyte recruitment,[6] while inducing polymorphonuclear-cell apoptosis.[6,75] Macrophages are hence attracted toward the tumor where they are integrated and where they represent the major inflammatory component of the stroma as TAMs.[5] These appear to predominantly comprise an M2 population, thus promoting angiogenesis, tissue remodeling and repair.[5,76] IL-6 together with CCL2 induces such an M2-type macrophage polarization.[77,78]

In the physiological regulation of inflammation, IL-6, along with the other major inflammatory cytokines IL-1, IL-12, and TNF-α, is downregulated by IL-10,[25] which is supposed to induce the termination of the inflammatory response. Studies of co-cultures of macrophages and colon cancer cells indicated that tumor cells first stimulated macrophages to produce IL-6, which was then followed by IL-6-induced IL-10 production by the tumor cells.[24] In cancer patients, this physiological negative feedback between these cytokines appears to be dysfunctional since a concomitant hyperactivation of both IL-6 and IL-10 is often apparent (Reviewed in[1])

In summary, IL-6 appears to be part of a cytokine network that regulates inflammation by triggering a consolidated phase through monocyte recruitment with a direct effect on the organization and integration of TAMs, which are essential components of the tumor structure. Solid tumors contain substantial amounts of non-malignant stromal cells, predominantly macrophages, lymphocytes, endothelial cells and fibroblasts.[79,80] In this context, IL-6 appears to have a formative role in the process of the chronic cancer-related inflammation, which becomes a genuine component of the tumor and the associated systemic reaction.

Source of IL-6

IL-6 is produced in a variety of cells, including fibroblasts, endothelial cells, keratinocytes, macrophages, T cells and mast cells.(Reviewed in[81]) Although IL-6 can also be produced by cancer tissue[82,83] and cancer cell lines[65,84-86] and IL-6 mRNA was detected in tumor cells,[87,86] the serum expression of IL-6 does not necessarily correlate with the tissue expression of IL-6.[88] High levels of IL-6 in the ascitic fluid of ovarian cancer patients was measured while IL-6 mRNA was not detected in tumor cells.[44] IL-6 was predictive for survival in elderly patients with chronic lymphocytic leukemia (CLL), while a corresponding IL-6 secretion by CLL cells was not found.[89] Similarly, the tumor cell expression of IL-6R was measured as a surrogate marker for IL-6 in a study of renal cell carcinoma, and was not significantly associated with circulating levels of CRP. This was interpreted as an indication that the main source of IL-6 responsible for an elevated CRP level in these patients was unlikely to be the tumor itself.[90]

Hence, an increased serum IL-6 is not necessarily related to an increased tumor cytokine production. As a potential alternative source, monocytes were shown to produce significantly higher levels of IL-6 in in cachectic cancer patients compared with healthy controls,[91] and pancreatic cancer cells were able to stimulate IL-6 production in peripheral blood mononuclear cells by 14-fold.[92] Similarly, monocytes in head-and-neck cancer patients have been reported to secrete higher levels of IL-6 than monocytes from control individuals.[93] As a consequence, it is so far unsolved if the increased IL-6 serum level in cancer patients is a function of an increased tumor cytokine production or the result of a systemic immune reaction. However, independent of the source, the resulting increase of IL-6 has a systemic impact.

Throughout the variety of cancer types, IL-6 appears to be linked to the patients' prognosis as a common denominator of the clinical deterioration. This allows a novel perspective on the ultimately lethal systemic paraneoplastic process, and new treatment alternatives could be directed against the resulting systemic paraneoplastic syndrome.

Clinical options?

Being part of an intricate network of cytokine interactions, it is highly unlikely that IL-6 alone is responsible for the clinical deterioration in cancer patients. IL-6 rather reflects a cascade of interdependent cytokines.[1] Hence, it is so far unknown if IL-6 has a causative role in the clinical deterioration in cancer patients or if it represents a mere epiphenomenon. The consist relation between the IL-6 serum level and clinical condition could possibly provide a non-invasive instrument in the long-term follow-up of cancer patients and could potentially be used for an initial assessment of treatment effects. Provided these retrospective and unselected data from the literature can be confirmed in future prespective analyses, IL-6 could be an indicator for a clinical cascade of events that may be relevant both in a diagnostic and a therapeutic environment.

Since IL-6 could be the 'end-product' of a cancer-induced chain of events and may not have an impact of its own, it is unclear if the pharmaceutical downregulation of IL-6 would be promising for cancer patients. However, several options exist already: in keratinocytes, nicotinamide appears to downregulate the gene expression of IL-6 (and IL-10).[94] Furthermore, drugs such as adalimumab and methotrexate suppress the serum IL-6 level (in rheumatoid arthritis patients).[95] Tocilizumab is a humanized monoclonal antibody acting as an IL-6 receptor antagonist and is used in the treatment of patients with rheumatoid arthritis. Tocilizumab inhibits both classic signaling and trans-signaling of IL-6. Pooled and meta-analyses

demonstrated efficacy and tolerability even during long-term therapy,[96] but unexpectedly these improvements were accompanied by increases in serum levels of IL-6 and IL-6R, possibly due to changed bioavailability.[97] The potential impact of IL-6 modifying medications on the paraneoplastic symptoms in cancer patients is yet to be established.

Conclusion

IL-6 is one component of a complex cancer-induced cytokine cascade. In the vast majority of clinical studies in cancer patients, the IL-6 serum level is increased. The increase of the IL-6 serum level appears to be a late-stage phenomenon in cancer patients and reflects a tumor-histology-independent systemic phenomenon. The available literature suggests a correlation between IL-6 serum level and the survival of cancer patients. Future studies will have to analyze correlations between individual IL-6 serum levels and prognosis on a larger scale in order to determine if IL-6 has a causative role in the clinical deterioration of cancer patients or if the IL-6 serum level is a mere epiphenomenon.

Article selection and analysis

To identify eligible studies, systematic searches of IL-6 in cancer patients were conducted using the PubMed database. Specifically, the search was filtered according to "prognostic impact of IL-6 in cancer patients" with the publication year after 1993 (until 2013) using the following algorithm:

(((((((Il-6[Title/Abstract]) AND Cancer[Title/Abstract]) AND survival[Title/Abstract]) AND patients[Title/Abstract]) AND ("1993"[Date - Publication] : "3000" [Date - Publication]))) OR (((((interleukin-6[Title/Abstract]) AND Cancer [Title/Abstract]) AND survival[Title/Abstract]) AND patients [Title/Abstract]) AND ("1993" [Date - Publication] : "3000" [Date - Publication]))) OR (((((Il-6[Title/Abstract]) AND lymphoma[Title/Abstract]) AND survival[Title/Abstract]) AND patients[Title/Abstract]) AND ("1993" [Date - Publication] : "3000" [Date - Publication]))) OR (((((interleukin-6[Title/Abstract]) AND lymphoma[Title/Abstract]) AND survival [Title/Abstract]) AND patients[Title/Abstract]) AND ("1993" [Date - Publication] : "3000" [Date - Publication])).

Disclosure of potential conflicts of interest

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