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The predictive value of interleukin-8 (IL-8) in hospitalised patients with fever and chemotherapy-induced neutropenia

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ABSTRACT

Aim: To demonstrate whether serum Interleukin-8 (IL-8) is a relevant parameter to select hospitalised patients with chemotherapy-induced neutropenic fever with low or high probability of infection.

Results: 90 assessable febrile episodes in 73 patients were evaluated; 46% of the febrile episodes were microbiologically documented infection (MDI), 8% clinical documented infection (CDI), and 47% fever of unknown origin (FUO). Median IL-8 level was lower in the FUO group compared to CDI and MDI ($p < 0.0005$). In 45 of 48 episodes (94%) with CDI/MDI, IL-8 level at the start was $\geqslant$60 ng/l while in 18 of 21 episodes (86%) with IL-8 level <60 ng/l, no infectious cause was demonstrated. FUO and CDI/MDI patients with IL-8 $\geqslant$60 ng/l and responsive on antibiotic treatment showed a decline of IL-8 levels within days in contrast to non-responding patients.

Conclusions: Serum IL-8 level can be a useful marker to identify hospitalised FUO patients with low probability of infection.

1. Introduction

Bacterial and fungal infections are frequently noticed during chemotherapy-induced neutropenia. The neutropenia and the disruption of the mucosal barrier as a consequence of the applied chemotherapy regimen predispose patients to a bacterial infection.[1] In the past, gram-negative bacteria were mostly responsible for infections in neutropenic patients. Nowadays, the majority of the infections are due to gram-positive microorganisms.[2,3] Because an infection in immunocompromised patients can be fatal in a short time, most patients with chemotherapy-induced neutropenia and fever are treated empirically with broad spectrum antibiotics. However, only part of the patients, ranging between 30 and 70%, demonstrate a microbiologically or clinically proven infection, suggesting that not all patients require antibiotic treatment.[4–8] Recently, it was demonstrated that patients presenting with fever and neutropenia in the outpatient setting can be categorised in subgroups with a high or low probability of infection.[9] Absence of clinical and physical abnormalities and an IL-8 level below 60 ng/l had a low probability of infection. Hospitalised patients are treated more aggressively with chemotherapy and have a more profound and more prolonged period of neutropenia in comparison to outpatients. Therefore, we investigated prospectively whether IL-8 in combination with C-reactive protein (CRP) and clinical parameters might also be helpful in selecting hospitalised patients with neutropenic fever with high or low risk features.[9]

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2. Patients and methods

2.1. Patients and definitions

All subsequent hospitalised patients older than 18 years with a haematological malignancy who developed chemotherapy-induced neutropenia and fever were enrolled in the study after informed consent. Chemotherapy-induced neutropenia was defined as an absolute neutrophil count in the peripheral blood of $<0.5 \times 10^9$/l, or $\leqslant 1.0 \times 10^9$/l and decreasing as a result of the applied chemotherapy. Fever was defined as a single, not otherwise explained, axillary temperature reading of $\geqslant$38.5 °C, or 38.0 °C for at least 24 h. Normalisation of temperature was a persistent temperature below 37.5 °C. When a causative agent was isolated, an infection was defined as microbiologically documented infection (MDI). For the diagnosis of coagulase-negative staphylococcal bacteraemia, at least two positive blood cultures were required. A clinically documented infection (CDI) was defined as an infection based on clinical or radiological signs of infection, but without isolation of a pathogen. A febrile episode which was neither MDI nor CDI was considered to be fever of unknown origin (FUO). The study was approved by the Medical Ethics Committee of our institution.

2.2. Study protocol and interventions

Before starting with i.v. antibiotics, all patients underwent a physical examination and radiological evaluation (X-rays of chest and sinuses); blood samples were taken for bacterial cultures, and determination of IL-8, measured by an immunochemiluminescence analyser (IMMULITE; DPC Biermann, Bad Nauheim, Germany), and CRP were performed. The cut-off value for IL-8 was 60 ng/l, based on a previous study on outpatients.[9] Two blood cultures from a peripheral vein were drawn at least 20 min apart. In addition, cultures from every lumen of the central venous catheter (CVC) and, on indication, other sites (urine, sputum, faeces, wounds) were performed. All patients with fever were started immediately with broad spectrum i.v. antibiotics, mainly piperacillin-tazobactam, and continued treatment until the 5th afebrile day, i.e. intervention was not guided by IL-8 values. Treatment was adapted according to culture results. In case of persistent fever without isolation of a pathogen, antifungal medication (itraconazole or voriconazole) was added on day 4. IL-8 and CRP monitoring was repeated at days 1, 3, 5 and 7.

2.3. End points

The primary end point was the presence or absence of an infection in relation to the IL-8 or CRP level. The secondary end point was the change in IL-8 level according to the response to treatment, i.e. normalisation of the temperature. In addition, the best cut-off value of IL-8 according to the receiver-operating curve (ROC assay) in hospitalised neutropenic patients was re-evaluated.

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows, version 14.0. Patient characteristics and end points were compared using χ^2 and Mann–Whitney U test. A two-sided P value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

The included patients suffered from acute leukaemia, lymphoma, or multiple myeloma and were all treated with intensive chemotherapy according to ongoing protocols (Table 1). They had a median age of 52 years (mean 49 years, range 19–73) and they all had severe leucopenia, median 0.2×10^9/l, and neutropenia, median 0.1×10^9/l (Table 1). All patients had a CVC in the subclavian vein and received prophylactic oral antibiotics and anti-fungal drugs for selective gut decontamination.[10] One hundred and five febrile episodes were documented, 15 episodes were not eligible because the IL-8 measurement was not performed in time (i.e. the day of fever or the following day) ($n = 10$) or because neutropenia was not present ($n = 5$). Ninety neutropenic episodes were evaluated in 73 patients. Microbiological examination demonstrated a positive blood culture in 46% of the episodes; this included gram-positive bacteria in 78% ($n = 32$), gram-negative bacteria in 20% ($n = 8$), and yeasts in 2% ($n = 1$) of the positive cultures (Table 2). More than half of the infections (22 of 41, 54%) were CVC-related. In 16 episodes (39%), bacteraemia without catheter infection was demonstrated (Table 2). In seven febrile episodes (8%) a CDI was present. In these febrile episodes abnormalities were seen on X-rays of the chest ($n = 3$), sinuses ($n = 1$), and a CT scan of the abdomen ($n = 1$). In two febrile episodes mucositis was observed during physical examination (Table 2). Based on these findings (Table 3), the patients were categorised as having FUO ($n = 42$, 47%), CDI ($n = 7$, 8%), or MDI ($n = 41$, 46%).

3.2. IL-8 and CRP levels at inclusion

A great variability in IL-8 serum levels was observed, ranging from 5 to 39,710 ng/l with a median of 148 ng/l. In 23% of the

Table 1 – Baseline characteristics of febrile episodes.

(A)		
Sex	Male	56 (62%)
	Female	34 (38%)
Underlying disease	Acute leukaemia	49 (54%)
	Lymphoma	20 (22%)
	Multiple myeloma	12 (13%)
	Other	9 (10%)
Treatment	Intensive Chemotherapy	53 (59%)
	Autologous SCT	29 (32%)
	Allogeneic SCT	3 (3%)
	Other	5 (6%%)
(B)		
Age (years)[a]	52	19–73
IL-8 (ng/l)[a]	148	5–39,710
CRP (mg/l)[a]	128	5–302
Leucocytes ($\times 10^9$/l)[a]	0.2	0.1–7.2
Granulocytes ($\times 10^9$/l)[a]	0.1	0.1–1.0

SCT: stem cell transplantation.
a Median; range.

Table 2 – Causes of clinically documented infections (CDI) and microbiologically documented infections (MDI).

CDI (n = 7)		
Pneumonia		3
Sinusitis		1
Mucositis		2
Colitis		1
MDI (n = 41)		
Infectious agents:	Gram-positive bacteria	32(78%)
	Gram-negative bacteria	8(20%)
	Yeast	1(2%)
Source of infections:	Catheter related	22(54%)
	Bacteraemia	16(39%)
	Typhlitis	1(2%)
	Meningitis	1(2%)
	Soft tissue infection	1(2%)

febrile episodes, the IL-8 level was less than 60 ng/l (Table 3). A significant difference in median IL-8 was demonstrated in FUO (70 ng/l, interquartile range 27–187) versus CDI and MDI (214 ng/l, interquartile range 137–545, $p < 0.0005$, Fig. 1A). In FUO episodes, IL-8 was <60 ng/l in 18 of the 42 febrile episodes (43%). Non-FUO episodes showed serum IL-8 levels $\geqslant$60 ng/l in 45 of 48 febrile episodes (94%), i.e. in three patients (6%) with a presumed infection, the IL-8 levels were below the cut-off point (Table 3). No difference in IL-8 level was shown in patients with a gram-negative (median 249 ng/l, interquartile range 159–995) versus gram-positive bacteraemia (median 214 ng/l, interquartile range 122–545, $p = 0.48$). In patients with IL-8 <60 ng/l, the median leucocyte count was significantly higher, but the absolute neutrophyl count was equal between the groups with a high or low serum IL-8 level (Table 3).

In the same group of patients, CRP levels were determined at inclusion and during follow-up. In the febrile group with IL-8 <60 ng/l, the median CRP level at day 1 was significantly lower (78 mg/l, range 5–175) than in febrile episodes with IL-8 $\geqslant$60 ng/l (142 mg/l, range 46–302, $p = 0.002$) (Table 3). The median CRP at day 1 in FUO versus the combined group of CDI and MDI was not significant different (105 versus 141 mg/l, $p = 0.06$).

3.3. *Response to antibiotic treatment*

In all episodes with chemotherapy-induced neutropenic fever, broad spectrum antibiotics were given, mainly piperacillin-tazobactam. Both in FUO and CDI/MDI a decline in serum IL-8 levels was shown in the responder group. Normalisation of temperature (i.e. persistently below 37.5 °C) after 3 days of treatment was noticed in 20 of 42 (48%) episodes with FUO, and in 10 of 48 (21%) episodes with CDI or MDI ($p = 0.045$). After 5 days of treatment, normalisation of temperature was shown in 67% of FUO patients and 38% of CDI/MDI episodes, respectively ($p = 0.008$). In 52% of the episodes with serum IL-8 <60 ng/l at inclusion, the temperature was normalised at day 3, which was the case in 28% of the episodes with serum IL-8 $\geqslant$60 ng/l ($p = 0.034$, Fig. 1B). Both responding patients with FUO ($n = 10$) or CDI and MDI ($n = 9$) who had an IL-8 level $\geqslant$60 ng/l at start showed a quick decline in IL-8 below 60 ng/l with a median decline of 92% and 72%, respectively. A median decline of CRP in these cases was 66% and 19%, respectively. In the non-responders with an IL-8 level $\geqslant$60 ng/l at the start ($n = 50$), the decline in IL-8 was less pronounced, 18% for FUO ($n = 14$) and 65% for CDI/MDI ($n = 36$) and IL-8 remained above the threshold value of 60 ng/l (104 and 113 ng/l, respectively). A decline of 8% in CRP levels was seen in non-responding FUO episodes with an IL-8 level $\geqslant$60 ng/l at the start, and in non-responding CDI/MDI episodes with an IL-8 level $\geqslant$60 ng/l at the start, a rise of 33% was seen. In three febrile episodes the outcome was fatal, all of them due to infection (one CDI and two MDI).These patients had an IL-8 level $\geqslant$60 ng/l at the start and during follow-up. None of the patients with IL-8 level <60 ng/l succumbed.

3.4. *Re-evaluation of IL-8 levels based on ROC analysis*

ROC analysis showed an IL-8 level of 20 ng/l as cut-off point for infection with a sensitivity of 95%. Only in nine febrile episodes (10%) was IL-8 level at inclusion <20 ng/l.

4. Discussion

In the hospital setting, patients with chemotherapy-induced neutropenic fever are generally treated with broad-spectrum antibiotics (also during episodes when no abnormalities can be diagnosed by physical examination or X-rays). In most studies, a clinically or microbiologically documented infection is shown in only half of the patients during the following days, consistent with a diagnosis of FUO in half of the patients.[4–8] Whether these FUOs represent an infection and need antibiotic treatment is questionable. A recent study in the outpatient setting indicated that the serum IL-8 level, using a cut-off level of 60 ng/l, might be an important

Table 3 – Patients characteristics with high (>60 ng/l) and low (<60 ng/l) IL-8 serum level at presentation.

		IL-8 <60 ng ($n = 21$)	IL-8 $\geqslant$60 ng ($n = 69$)	P-value
Febrile episodes:	FUO ($n = 42$)	18	24	
	CDI ($n = 7$)	0	7	
	MDI ($n = 41$)	3	38	
Age (years)[a]		59 (23–73)	51 (19–71)	0.075
CRP (mg/l)[a]		78 (5–175)	142 (46–302)	0.002
Leucocyte ($\times 10^9$/l)[a]		0.6 (0.1–5.9)	0.1 (0.1–7.2)	0.002
Granulocytes ($\times 10^9$/l)[a]		0.1 (0.1–0.3)	0.1 (0.1–1.0)	0.380

FUO: fever of unknown origin; CDI: clinically documented infection; MDI: microbiologically documented infection.
a Median; range.

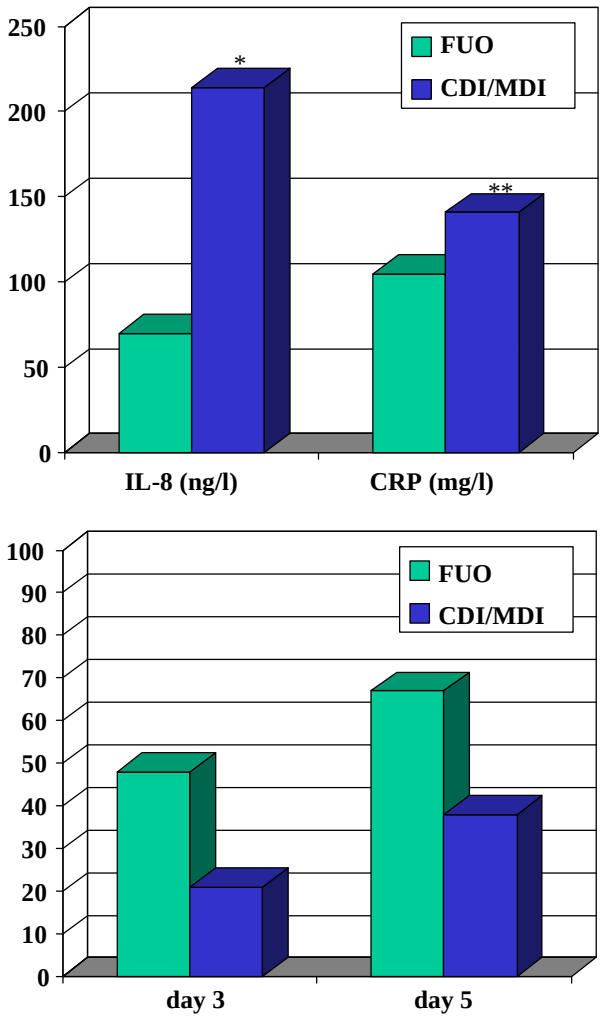

Fig. 1 – (A) Median interleukin-8 (IL-8) and C-reacting protein (CRP) in patients with fever of unknown origin (FUO), clinical documented infection (CDI) or microbiologically documented infection (MDI) at presentation; *$p < 0.005$; **$p = 0.06$. (B) Response percentage following 3 and 5 days of intravenously applied antibiotic treatment in patients with an interleukin-8 (IL-8) of <60 ng/l or >60 ng/l at presentation.

parameter for categorising patients with a low or high probability of having a bacterial infection.[9] In a recent inpatient study it was shown that IL-8 levels also had a predictive value for discriminating patients with bacteraemia.[8] However, a threshold level for IL-8 of 1000 ng/l was used which was noticed in only 7% of the patients. The results of the present study demonstrate that FUO and CDI or MDI were documented in 47% and 53% of the studied febrile episodes. These findings are comparable with results of other studies.[4–8] An IL-8 level <60 ng/l was predominantly shown in patients with FUO. In three febrile episodes (6%) with CDI/MDI the serum IL-8 level was <60 ng/l. All these patients had a MDI with coagulase-negative staphylococci related to an infected CVC and showed an increasing IL-8 level during the following days. These findings indicate that in only 6% was the IL-8 serum level of 60 ng/l not a reliable predictor for a definite bacterial infection in this patient subpopulation. In 18 febrile episodes of 21 with an IL-8 level <60 ng/l, FUO was observed. ROC analysis revealed that the predictive value of serum IL-8 level could be improved by using a cut-off value of 20 ng/l instead of the actual IL-8 cut-off level used.[9] However, this would strongly reduce the clinical applicability of the assay since only 10% of the patients showed an IL-8 level <20 ng/l. We prefer using the cut-off value of 60 ng/l and repeating the IL-8 determination at day 3, thereby increasing the sensitivity of the assay.

Another reason to determine IL-8 not only at the start of fever, but also at day 3, is the early documentation of response to the chosen antibiotic regimen. Responsive patients showed a quick decline in IL-8 even before normalisation of the temperature. In this subgroup of patients, it might be interesting to examine whether the number of days on systemic antibiotics could be reduced. Similarly, whether a rise in IL-8 levels at day 3 has to be considered as a therapy failure and has to be translated in a switch in the applied antibiotic regimen could be further investigated.

Patients with FUO showed a significantly faster response upon antibiotic treatment after 3 to 5 days of treatment compared to patients with CDI/MDI. The faster treatment response was not related to a higher granulocyte count which is an important determinant for responsiveness. A previous study has shown that IL-8 is predominantly produced by endothelian cells during neutropenic fever.[11]

In comparison to CRP, the IL-8 level seems to be more worthwhile for discriminating infectious from non-infectious causes in neutropenic febrile patients, especially at the start of the febrile episode. The kinetics of CRP levels showed a slower response pattern. The rise in CRP levels is generally seen at a later time point than the maximum IL-8 level. Similarly, the decrease in CRP level was slower in time in comparison to the decline in IL-8. Moreover, CRP is less specific for infectious episodes than IL-8.[12,13]

These findings indicate that measurement of IL-8 in the clinical setting might contribute to categorise FUO patients with a low probability of infection especially when follow-up measurements are performed 2 or 3 days later. Prospective studies will demonstrate whether FUO patients with IL-8 <60 ng/l might be followed without antibiotic treatment unless a bacterial infection is detected. Similarly, IL-8 measurements might obtain a more prominent position for defining whether or not a patient responds to antibiotic treatment.

Conflict of interest statement

None declared.

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