Inflammatory Markers in Patients after Hematopoietic Stem Cell Transplantation

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Received: 19 June 2012 / Accepted: 25 March 2013 / Published online: 7 April 2013
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Abstract Infections are one of the most common complications after hematopoietic stem cell transplantation (HSCT). Diagnosis is established by analysis of clinical symptoms and results of diagnostic tests such as biochemical panels, microbiological cultures, and visual diagnostics. As the microbiological cultures yield positive results in only some patients and visual diagnostics might miss the infectious source, the diagnosis and proper treatment often depends on clinical assessment supported by laboratory test results. The most commonly used makers of inflammation include C-reactive protein and procalcitonin. However, these tests have serious limitations when used in patients after HSCT. The drugs used in conditioning, neutropenia, and graft-versus-host disease might influence the results of the tests and misguide the physician. In this review, we summarize the current knowledge on profiles of expression of basic markers of inflammation used in clinical practice in patients after HSCT.

Keywords C-reactive protein · Procalcitonin · Hematopoietic stem cell transplantation · Infection

Abbreviations

aGvHD	Acute graft-versus-host disease
ATG	Antithymocyte globulin
BMT	Bone marrow transplantation
CRP	C-reactive protein
FUO	Fever of unknown origin
GvHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplantation

MTC	Major transplant-related complication
PCT	Procalcitonin
TBI	Total body irradiation

Introduction

Hematopoietic stem cell transplantation (HSCT) allows successful treatment of many hematologic malignancies and nonmalignant disorders. The curative potential of this procedure and survival of the patients is limited by infection, the recurrence of the disease and by graft-versus-host diseases (GvHD) in allogeneic transplant recipients. The infection risk is elevated as a result of substantial alteration of the function of the immune system, caused by prior treatment and transplantation. Moreover, the complications of the transplantation such as GvHD and the resulting treatment might lead to further immunosuppression and increase the risk of severe infections. An early detection and treatment of infection is essential to decrease morbidity and mortality in severely immunocompromised patients. Defining the pathogenesis of transplant-related complications and differentiating them is often problematic due to unspecific clinical signs and symptoms during their presentation. The blood cultures might be negative even during severe sepsis and visual diagnostics will not always be of use. However, monitoring the serum levels of infection biomarkers before and after HSCT may predict the occurrence of transplant-related complications and provide guidance for proper treatment (Azarpira et al. 2009). There is no single ideal marker that allows the distinction of infection from other complications with early and specific diagnosis. So far, the markers have limited ability to predict outcome in specific cases, which is quite

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often compromised by concomitant medication or complications. Assays of cytokines, peptides, and acute phase proteins in different periods of neutropenia might be helpful for early risk assessment of severe infections and inflammation. C-reactive protein (CRP) and procalcitonin (PCT) are some of the most commonly used markers for this purpose.

Many researchers question the clinical significance of the use of biomarkers in the neutropenic patients. The data gathered so far has limitations regarding sample size and heterogeneity of the study populations (Azarpira et al. 2009; Massaro et al. 2007). Even though advances in the field of HSCT have been made, challenges still remain for clinicians and researchers to conduct accurately designed studies to better describe the risk factors, epidemiology, and measures for prevention of transplant-related infections (Magauran and Salgado 2011). In this review, we address the current knowledge about common infection markers, CRP and PCT in the patients undergoing HSCT, addressing the usefulness and limitations in various clinical situations.

Inflammation Markers During Transplantation-Specific Phases

Conditioning

Although CRP and PCT are established markers of infection in the general population, their utility in patients undergoing HSCT might be influenced by many factors. The conditioning phase which precedes transplantation during which patients receive pharmacological agents alone or with total body irradiation (TBI) results in profound neutropenia and immunosuppression. However, only a few substances have an influence on the synthesis of basic inflammation markers. The most common drug used during the conditioning that strongly influences inflammation marker levels is antithymocyte globulin (ATG). It is a mixture of antibodies against T cells which is used in the prevention and treatment of acute rejection in organ transplantation, and therapy of aplastic anemia. Side effects associated with ATG administration are common and include inflammatory reactions with fever and chills, impaired renal function, thrombocytopenia, leukopenia, skin rashes, circulatory instability, respiratory insufficiency and release of inflammation markers (Brodzka et al. 2009; Dornbusch et al. 2003; Pihusch et al. 2002). These reactions vary in intensity among different patients and in some cases may resemble sepsis. ATG might trigger a characteristic early surge of CRP and PCT without associated clinical or microbiological evidence of infection, the initial rise of these markers can be as high as 5- to 50-fold over

the initial values depending on the patient and the dose of ATG used (Brodzka et al. 2009). In a study by Brodzka et al. (2009), both CRP and PCT increased significantly 1 day after the beginning of ATG administration. The increase of the markers was usually transient and followed by a steady decline over the course of 3 days to almost baseline levels on day 4. The dynamics of the two markers were similar, CRP returning to baseline levels 1 day earlier than PCT. This early surge was usually not associated with clinical infection, as monitored by microbiological cultures; however, the CRP and PCT could not be used to make any speculations about possible infections at that time. Furthermore, the levels of PCT after the ATG did not correlate with the risk of developing infection. If the patients develop sepsis after the ATG conditioning, the changes in CRP and PCT concentration do not behave in a uniform manner depending on severity of infection and the treatment. The postulated mechanism of induction of infection markers by ATG is connected primarily to the direct effect on T lymphocytes and also possibly the hepatotoxicity of the drug and cytokine release syndrome (Brodzka et al. 2009; Pihusch et al. 2002).

In an interesting study on intestinal damage after conditioning by van der Velden et al. (2010), CRP and citrulline levels were measured after six different types of conditioning regimens. Five myeloablative regimens and one non-myeloablative conditioning regimen were included in the study. ATG-containing conditioning was the only one that caused the surge of CRP values over 50 mg/L. Other conditioning protocols analyzed retrospectively containing cyclophosphamide, TBI, high-dose melphalan, bendamustine, etoposide, adriamycin, fludarabine, cytarabine or idarubicin were unable to induce elevation of CRP to the levels seen in infection. The CRP synthesis increased significantly, but usually remained under 50 mg/L and there was no single patient that crossed over 100 mg/L. The CRP and PCT should be used with precaution during administration of most of the conditioning regimens which do not contain ATG as a specific marker of infection; however, the specificity and sensitivity in that setting has to be further analyzed. The use of ATG in conditioning regimens renders CRP and PCT useless as markers of infection, however, this effect is only temporary and after the levels decrease, the markers can be used again (van der Velden et al. 2010). The CRP response during different conditioning regimens is shown in Fig. 1.

Aplastic Phase of HSCT

The risk of infection increases when the patient enters the aplastic phase of the hematopoietic stem transplantation. The standard procedures at this phase include antibacterial, antifungal and antiviral prophylaxis and monitoring of

Fig. 1 Summary of the time course of CRP in different conditioning regimens. Day 1 is the day of start of conditioning. 1 High-dose melphalan, 2 BEAM, 3 idarubicin-cyclophosphamide (Cyclo)-TBI, 4 Cyclo-ATG-TBI, 5 Cyclo-TBI, 6 Cyclo-fludarabine. Mean CRP in mg/L (reprinted from van der Velden et al. 2010)

inflammation markers. At the onset of fever, blood cultures are taken and usually antibiotic treatment is initiated. The infection markers in this period play an important role. Most centers provide constant monitoring where CRP values are measured every 2 days. These serial measurements of CRP might be useful in identifying patients with developing infections and determining the course of infection as the CRP values increase before the infection becomes clinically apparent. Ortega et al. (2004) observed in their study that the CRP level on the first day of fever during the neutropenic period does not allow differentiation of the etiologies of the febrile episode. Persistently high values, however, were associated with an unfavorable outcome of any febrile infectious episode (Ortega et al. 2004). CRP value equal to or higher than 160 mg/L on the fifth day of fever was associated with an unfavorable outcome and a higher risk of death due to an infectious etiology. This was with a sensitivity of 100 %, a specificity of 87 %, a positive predictive value of 30 % and a negative predictive value of 100 % (Ortega et al. 2004). However, due to the possibility of elevated baseline levels of CRP and longer time needed to peak its concentration, it is postulated to be used for monitoring rather than for rapid diagnosis of infection.

Hambach et al. (2002) reported that the difference of maximal PCT levels during bacterial or fungal infections in aplasia and non-aplasia was not significant. Moreover, they could see a correlation between PCT levels and severity of the systemic inflammatory reaction. The influence of

aplasia and severe immunosuppression on these characteristics of PCT has not been thoroughly studied (Hambach et al. 2002). Hambach et al. (2002) compared the diagnostic value of PCT with that of CRP in detecting infections and other treatment-related complications after allogeneic stem cell transplantation (SCT). They concluded that PCT did not have a superior diagnostic value to that of CRP in the detection of bacterial or fungal infections after allogeneic SCT. In this setting, PCT is more superior in reflecting the extent of the systemic reaction than its underlying cause.

Concentrations of both PCT and CRP are high during bacterial and fungal infections (median 2.3 and 188 mg/L), moderately elevated during FUO (median 1.5 and 82 mg/L), and low during clinical events where evidence of bacterial and fungal infections could not be found (median 0.4 and 55 mg/L) (Hambach et al. 2002). The cut-off concentration for best prediction of bacterial/fungal infections is a maximum PCT of over 1 µg/L, maximum CRP of over 100 mg/L, increase (Δ) of PCT of over 1 µg/L, and an increase of CRP of over 50 mg/L. What is interesting is that observed CRP levels started to increase before the clinical signs appeared, while PCT levels usually increased on the next day after onset of bacterial or fungal infection and peaked shortly thereafter. The CRP levels seem to be the most sensitive marker of systemic infection in neutropenic patients increasing often before the clinical signs of infection become apparent (Hambach et al. 2002). If the patients were successfully treated, it took around 4 days for the PCT values to return to baseline. CRP reached its peak concentration after a median of 3 days (range 0–10 days) and the next minimum levels 6 days after the increase of CRP levels (range 1–19 days). What is also interesting is that maximal CRP during bacterial or fungal infection in aplasia is significantly higher than during infections in non-aplastic phase (median values were 227 vs 145 mg/L) (Hambach et al. 2002). This might have been caused by the severity of infection that otherwise would have been at least in part controlled by the immune system.

Graft-Versus-Host Disease

Acute GvHD poses a major threat to the patients after allogeneic HSCT. It occurs when transplanted donor T lymphocytes react to foreign host cells antigens, resulting in a variety of host tissue injuries. Diagnosis of GvHD following HSCT may be a challenge as it shows similar clinical symptoms to other transplant-related complications. Diarrhea, hyperbilirubinemia, nausea, emesis, and skin rashes can be signs of GvHD as well as toxicity from medication or infection. Differentiating GvHD from other

complications with similar clinical symptoms requires invasive procedures, such as organ biopsies, which are usually time consuming, and which may also have limited sensitivity. Several biomarkers in patients with GvHD may reach abnormal levels, but their clinical significance is controversial. A variety of inflammatory cytokines are produced following conditioning, infections and engraftment, such as tumor necrosis factor α , interleukin (IL)-6, and IL-1, and they play a major role in activating T cells, subsequently leading to GvHD and tissue destruction. There is no clear evidence that CRP can be used and how it should be used to predict GvHD. The patterns of cytokine release are non-specific with regard to the subtype of MTC, and CRP may have limited value in specifically predicting GvHD (Schots et al. 2002; Fuji et al. 2008). Patients with maximum CRP levels of 150 mg/L or more in the neutropenic period were more likely to suffer from GvHD grades II–IV than patients with CRP levels below that threshold, showing a sensitivity of 37 % and a specificity of 75 % (Fuji et al. 2008). The samples were obtained before starting the conditioning regimen and routinely taken at least three times per week. The median day of maximal CRP level was day 10 (range 0–25). When only patients receiving myeloablative conditioning were included, 25 % grade II–IV acute GvHD (aGvHD) were seen in the low-CRP group, and 58 % in the high-CRP group, 7 % grade III–IV in the low-CRP group and 21 % in the high-CRP group (Fuji et al. 2008). In a study on leukemic relapse and its correlation with CRP levels, Min et al. (2006) found that mean CRP levels on the first and second weeks after transplant were significantly higher in those with aGvHD and chronic GvHD than in those patients without GvHD (mean $\pm$ SE 72.3 $\pm$ 13.3 vs 35.7 $\pm$ 6.0 mg/L for first week; 57.7 $\pm$ 10.0 vs 24.8 $\pm$ 3.2 mg/L for second week). There were, however, no significant differences with regard to the CRP levels in these patient groups on the third and fourth weeks (mean $\pm$ SE 19.8 $\pm$ 3.8 vs 15.7 $\pm$ 2.2 mg/L for third week; 9.1 $\pm$ 2.1 vs 7.2 $\pm$ 0.9 mg/L for the fourth week). The CRP levels were measured weekly. In this study, the early rise of CRP after transplant may not only be a marker of GvHD but also the graft-versus-leukemia effect (Min et al. 2006). Antigen-activated T cells are not only involved in GvHD and graft rejection, but also leukemia control and protection against infectious agents (Min et al. 2006).

On the other hand, some authors report the lack of association between CRP levels and exclusive GvHD (Pihusch et al. 2006; Saarinen et al. 1987; Schwaighofer et al. 1994). Schwaighofer et al. (1994) observed increased CRP levels after bone marrow transplantation (BMT) during severe infections or FUO, but not in the case of aGvHD grade III/IV. They measured CRP every second day from day –6 to day +86 in patients undergoing BMT. The

serum levels were further analyzed when complications after BMT occurred, such as aGvHD, FUO and severe infectious complications. The magnitude of the serum level peaks were related to further complications occurring later in the post-transplant period, and were high in patients with complications, and low in patients without complications. Serum levels returned to baseline 14 days after transplantation. A further increase was associated with infectious complications or FUO, but not with aGvHD grade III or IV. Since no increase of CRP was observed during GvHD, they hypothesized that CRP is not involved in the induction of GvHD and thus suggested that it might be used in the diagnosis of infectious complications after allogeneic HSCT (Schwaighofer et al. 1994). Pihusch et al. (2006) analyzed levels of CRP, PCT and IL-6 prior to conditioning and weekly until 8 weeks after HSCT. They also found that exclusive aGvHD did not elevate CRP levels (44 vs 57 mg/L). The same was true for PCT levels (0.8 vs 0.8 ng/L). In the studied patients CRP decreased during steroid therapy (61 vs 31 mg/L), but PCT did not (2.3 vs 2.0 ng/dL). They concluded that PCT can differentiate GvHD from infection despite steroid therapy. The aGvHD grade I–IV did not correlate with increasing CRP or PCT levels without steroids either. They did, however, notice that CRP levels until the second week were significantly elevated in patients who later developed aGvHD (40 vs 86 mg/L) compared with patients without signs of aGvHD later. The values of CRP and PCT were significantly elevated in patients with infections only, compared to those with exclusive aGvHD. Patients with signs of aGvHD and simultaneous infection, had higher CRP levels (125 mg/L) compared to patients without complications (vs 44 mg/L), but not when compared to patients with exclusive infection (vs 128 mg/dL). They suggest confirmatory trials using PCT as a marker for infection in patients with aGvHD and infection receiving steroids (Pihusch et al. 2006).

There is no clear answer to the question of whether or not CRP or PCT can be used as a marker of GvHD. The observation of correlation of elevated CRP levels in the first to second week after the transplantation and GvHD requires further studies. Do infections or other complications in that period lead to GvHD? Does preventing increases in CRP by antimicrobial therapy or other preventive measures lead to lower occurrences of GvHD in patients later on? The use, analysis and publication of data on CRP and PCT in GvHD studies should lead to better understanding of this phenomenon.

Engraftment Syndrome

Engraftment syndrome (ES) is a non-infectious pulmonary complication occurring around the time of neutrophil

recovery following HSCT. There are no uniform classification criteria available for this complication. It is characterized by non-infectious fever, weight gain, an erythrodermatous skin rash, and non-cardiogenic pulmonary edema (Spitzer 2001). The reported incidence of ES has varied widely, ranging from 7 % (Edenfield et al. 2000) to as high as 59 % (Lee et al. 1995). This is thought to be due to a lack of common diagnostic criteria (Carreras et al. 2010; Spitzer 2001). The lack of well-defined criteria for the diagnosis of ES has also likely influenced the analysis of risk factors for its occurrence (Spitzer 2001). The pathogenesis of ES remains unknown but it is thought that the local and systemic injury seen is a result of pro-inflammatory cytokines released during neutrophil recovery. Macrophage colony-stimulating factor, erythropoietin and products of neutrophil degranulation and oxidative metabolism, are also thought to be involved in the process (Spitzer 2001). Many cytokines have been implicated in the pathogenesis of ES; however, there has been no well-defined characterization of the cytokine profile on ES (Spitzer 2001). ES represents a form of diffuse capillary leak associated with pulmonary edema and lung injury. It is also called capillary leak syndrome, autoaggression syndrome, aseptic shock syndrome and peri-engraftment respiratory distress syndrome (Carreras et al. 2010). ES may manifest clinically as combinations of non-infectious fever and an erythrodermatous maculopapular skin rash mimicking aGvHD with pulmonary infiltrates, hypoxia and diarrhea. Other clinical manifestations reminiscent of capillary leak syndrome, such as edema, ascites, hypoalbuminemia, and weight gain, all occurring at the time of engraftment may also be seen (Lee et al. 1995; Maiolino et al. 2003; Rabinowitz et al. 1993). A combination of the clinical information listed above and high-resolution computer tomography findings may help confirm the diagnosis. Distinguishing ES from GvHD in the allogeneic setting has been difficult (Spitzer 2001). It is also a complex differential diagnosis in case of infections occurring at the end of the neutropenic period. This has a special relevance because ES responds dramatically to corticosteroids when they are administered early after the onset of symptoms. However, when incorrectly treated or when treatment is delayed, ES can evolve to an irreversible multiple organ dysfunction syndrome. Both the Spitzer and the Maiolino diagnostic criteria of ES are similar and consistent for the three most relevant symptoms and signs of this syndrome: non-infectious fever, skin rash, and pulmonary infiltrates with hypoxemia (Carreras et al. 2010; Maiolino et al. 2003; Spitzer 2001). The information about CRP dynamics in the setting of engraftment syndrome is very scarce. However, the study by Carreras et al. (2010) showed an excellent correlation between CRP levels and ES, and

these authors suggest that the Maiolino criteria may be helpful in detecting patients with ES, and in doubtful cases, the diagnosis could be confirmed by CRP evaluation. Patients with ES after HSCT may have varying elevations of levels of CRP. However, if the fever does not respond to antibiotics, cultures are negative and there is a sudden increase in CRP values; the authors believe it is enough evidence to establish the diagnosis and start appropriate therapy (Carreras et al. 2010). They observed elevated CRP levels in all ES cases (43 out of 328 patients after peripheral blood auto-SCT). This was not seen in the remaining patients at engraftment (median $\pm$ SD 175 ± 73 vs 24 ± 34 mg/L). Forty-two patients developed non-infectious fever including one or more clinical sign of ES within 7 days of engraftment. All patients had high levels of CRP, with some even reaching extremely high levels. All patients with ES showed a sudden increase in CRP values that was not observed among those without signs of ES at engraftment (mean $\pm$ SD: 175 ± 73 vs 24 ± 34 mg/L). CRP values presented during neutropenic fever were a median of three times (range 2–30) lower than those observed in the same patients when ES developed. After steroid treatment, CRP levels quickly returned to normal values in all cases except in one patient who died because of this complication. To determine the best value of CRP in order to discriminate patients with or without ES, a receiver operating characteristic analysis was performed. This analysis showed that a cut-off level of 60 mg/L had the best sensitivity (90 %) and specificity (90 %). When they reviewed CRP levels in the whole series, values as high as those observed in ES, were only observed in patients with severe bacterial or fungal sepsis. Thus, CRP may be a useful tool for establishing a correct differential diagnosis in patients with possible ES (Carreras et al. 2010). However, this data has to be perceived with caution since according to most publications (Spitzer 2001) CRP is not appropriate to distinguish between infection and engraftment. Therefore, the decision to start antibiotic therapy at this time should not be made based only on the levels of this marker.

Mucositis

The agents used in conditioning damage the rapidly dividing cells of the oral and gastrointestinal mucosa, initiating an inflammatory cascade which results in mucosal barrier injury (MBI), clinically manifested as mucositis (van der Velden et al. 2009). Several authors report oral mucositis to be correlated with worse clinical and economical outcomes after HSCT (Pico et al. 1998; Sonis 2011; van der Velden et al. 2009). Mucositis is an important risk factor for fever, infections, bacteremia and sepsis

since the mucosal disruption might lead to bacterial translocation of the endogenous oral flora. This is especially true in the neutropenic patient (Sonis et al. 2004; van der Velden et al. 2009). Oral mucositis is a frequently occurring toxicity, some reporting up to 75 % incidence in patients receiving high-dose conditioning regimens used for allogeneic SCT (Cutler et al. 2005). The overall frequency varies, however, and is influenced by factors such as age, diagnosis, type of conditioning regimen, dose, and frequency of drug administration (Pico et al. 1998). The ulcerative mucosal lesions cause pain, restrict oral intake, and may potentially compromise the efficacy of cancer chemotherapy, due to missed doses or subsequent dose reductions of therapeutic agents (Peterson and Cariello 2004; Pico et al. 1998; Sonis et al. 2004). Chemotherapeutic agents that are known to be mucotoxic include methotrexate, etoposide, cyclophosphamide, 5-fluorouracil, doxorubicin, melphalan, and cytosine arabinoside (Pico et al. 1998).

CRP has been shown to be elevated in radiation-induced mucositis in patients with head and neck cancer (Ki et al. 2009; Mohammed et al. 2012). Mohammed et al. (2012) reported from their study that CRP levels were significantly elevated by 6 weeks in a radiation-dose-dependent manner. Ki et al. (2009) also observed a correlation between the presence of acute mucositis and CRP levels. They were able to determine CRP levels together with mucosal reactions evaluation during or after radiotherapy to provide further information on radiation-induced mucositis. A change of the mean CRP level was correlated with progression of mean grade of mucositis according to radiation fraction number (Ki et al. 2009). The inflammation observed in mucositis does not necessarily have to be elicited by microbes, as the mucosal barrier disruption alone seems to be able to induce a systemic inflammatory response, evidenced by elevated CRP levels and fever (van der Velden et al. 2009). van der Velden et al. (2009) conducted a retrospective analysis in a cohort of 67 patients undergoing autologous HSCT. The aim was to explore the impact of oral and GI mucositis on the systemic inflammatory response. They observed that their patients, even when free of clinically or microbiologically identified infection, still had a significant inflammatory response. This could be seen by marked elevations of CRP, and an incidence of fever in up to 69 %. All the patients had significant mucositis of the gut and/or oral cavity. It seems as though the inflammatory response due to the evolving mucositis was associated with the microbial translocation and resultant bacteremia, as it preceded the bacteremia by 2 days. The patients were divided into two groups: those with bacteremia (30 patients) and those without a documented infection (16 patients). An inflammatory response coincided with the occurrence of significant mucositis in all

patients, regardless of the presence or absence of infection. CRP levels were measured every day and the maximal CRP values as well as the day of maximal CRP values were recorded. In both groups CRP levels were elevated for all patients starting on average 6 days post-HSCT, and reaching a maximum 10 days post-HSCT. The course was similar but there was a significant difference in the mean maximal CRP (193 vs 94 mg/L). The median day of onset of fever was 8 days post-HSCT in both groups, where all the bacteremic patients became febrile as well as 69 % of the patients without documented infection. Patients in both groups developed oral mucositis with a mean maximum Nijmegen Nursing Mucositis Scoring System score of 8.3 and 8.4, respectively, 8 days after the transplantation. The author's data showed a clear pattern of an inflammatory response, irrespective of the presence or absence of infection. This coincided with the occurrence of mucositis, although the magnitude of the inflammatory response can be aggravated by superimposed infection arising from the MBI and the coexisting neutropenia (van der Velden et al. 2009).

Conclusion

The most critical issue in the HSCT population of patients is the prevention of complications by rapid diagnosis of infection and its proper differentiation from other complications. CRP and PCT both provide important information to answer these questions. Synthesis of CRP and PCT occurs throughout the period of transplantation, including the aplastic phase (Schots et al. 1998) and theoretically both could be used to aid the proper diagnostics of patients after HSCT. Elevation of CRP before the transplantation is a risk factor of serious complications and in such situations patients should be carefully evaluated. Throughout the conditioning and aplastic phase, the CRP was shown to be a good marker of infection. The limitations include serious complications of HSCT such as mucositis, GvHD and engraftment syndrome where infectious markers are elevated and do not give critical data for the diagnosis of concomitant infections. The data regarding use of CRP and PCT for differentiation of major transplant complications come mostly from retrospective studies and is insufficient to draw far reaching conclusions. However, the sudden rise of CRP and PCT in patient after HSCT should always be carefully evaluated as it might suggest the development of a potentially fatal complication. More prospective studies on use of inflammation markers are needed in population of patients undergoing HSCT, especially in patients with acute GvHD where the possibility of rapid and simple differentiation between infection and reaction against self-antigens is needed.

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