Mucositis: from febrile neutropenia to febrile mucositis

Nicole M. A. Blijlevens1*, Richard M. Logan2 and Mihai G. Netea3

1Department of Haematology, Radboud University Medical Center, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands; 2Discipline of Oral Pathology, School of Dentistry, Faculty of Health Sciences, The University of Adelaide, Australia; 3Department of Medicine, Radboud University Medical Center, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands

The treatment of patients with cancer is often accompanied by life-threatening complications caused by chemotherapy and radiotherapy. They are known to result from neutropenia, but damage to the mucosal barrier as well as the humoral and cellular immune defences play a significant role in various infectious complications and aggravate diverse inflammatory processes. The article describes the journey from febrile neutropenia to febrile mucositis in patients treated with immunocompromising therapy.

Keywords: mucosal barrier injury, innate immunity, inflammation, cancer treatment, infections

Febrile neutropenia (FN)

The number of immunocompromised patients has increased over recent decades and is expected to rise further due to the use of existing and new immunosuppressive drugs. While dose escalation and more aggressive treatment modalities have resulted in improved rates of survival, this has been at the price of variable but profound deficiencies in host defence mechanisms. A combination of better supportive care by the transfusion of blood and stem cell products, applying antimicrobial agents and recombinant growth factors, has provided the conditions for this development.

Infection has emerged as the most prominent complication of cytotoxic therapy. More than 40 years ago, Bodey et al.1 showed a positive correlation between the severity and duration of neutropenia (defined as an absolute neutrophil count of \( <0.5 \times 10^9 \) cells/L or a count \( <1.0 \times 10^9 \) cells/L expected to fall below \( 0.5 \times 10^9 \) cells/L) and the risk of acquiring a life-threatening bacterial infection. In an immunocompromised patient, fever is often the first and only sign of infection. Thus, fever during neutropenia (the so-called ‘febrile neutropenia’) may indicate a life-threatening infection that, if untreated, could result in sepsis and even death. Schimpff et al.2 demonstrated convincingly that early empirical administration of antimicrobial agents (i.e. at the onset of fever) covering suspected life-threatening pathogens without waiting for the results of blood cultures saved lives, and this approach is now the standard of care. In most cases, fever, defined as a single oral temperature of \( >38.3^\circ C \) or a temperature of \( >38.0^\circ C \) for \( >1 \) h, serves as a trigger for action. Thus, FN is a determinant and predictor of outcome when treating patients with chemotherapy-induced neutropenia and is often used as the primary endpoint of many studies testing antimicrobial efficacy.

However, a substantial number of patients receiving empirical therapy remain febrile despite the absence of a documented infection.3 Such episodes of fever were designated ‘unexplained fever’ in patients who did not develop a microbiologically defined infection (MDI) or a clinically defined infection (CDI).4 Most doctors assume that ‘unexplained fever’ is, nonetheless, related to infection, the pathogens remaining undetected, possibly due to low numbers that escape detection when limited volumes of blood are being sampled for culture.

Numerous large studies have shown, in general, that monotherapy consisting of an anti-pseudomonal \( \beta \)-lactam is effective in the empirical treatment of uncomplicated first episodes of fever in neutropenic patients. Only half of the patients who develop fever during neutropenia will present with a CDI or an MDI, the majority being pulmonary infiltrates and bacteremia.5 Even vancomycin can be withheld empirically for treating persistent fever until the results of the cultures indicate otherwise. The meta-analysis by Vardakas et al.6 confirmed that the use of a glycopeptide did not reduce time to defervescence. Fever even persisted in over 50% of 114 patients after first being treated for 3 days with broad-spectrum empirical therapy and, in addition, randomized to receive 3 days with or without teicoplanin.7 Installing broad-spectrum therapy pre-emptively in stem cell transplant (SCT) patients could not prevent the occurrence of FN in over 90% of the patients but only significantly delayed the onset of fever by 1 day.8 An analysis of 95 trials performed between 1973 and 2004 unequivocally showed a significant reduction in infection-related mortality, CDI, MDI and bacteremia, especially with fluoroquinolone prophylaxis in patients.
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treated for haematological malignancies; nevertheless, FN still occurred in ~50% of the patients.9 The expected duration of neutropenia and subsequent risk of infection vary according to the extent of chemotherapy-induced myelosuppression but many other patient-related factors play a role and can be used to assign patients a high- or low-risk probability for these complications. Also the median time to defervescence varies with the risk group and may even lead to the safe withholding of antibiotics in selected low-risk febrile neutropenic patients.10 The use of white blood cell growth factors as primary prophylaxis to shorten chemotherapy-induced neutropenia is advocated in the treatment of patients with a solid tumour or lymphoma but even here ~20% of patients still develop FN.11

The results are not that clear in patients treated for leukaemia, as most studies have shown a shortening of the duration of neutropenia but no reduced incidence of FN. The incidence of FN in SCT recipients is very high but the duration of severe neutropenia is relatively short, ~10 days with the use of collected peripheral stem cells. The use of growth factors in SCT patients could not reduce the duration of fever,12 indicating that the duration of neutropenia is not always the only risk factor for infection. Even Bodey et al.1 had already acknowledged that the relationship between neutropenia and infection risk did not hold for febrile patients who were not infected and suggested that neutropenia was not the sole determinant of fever.

Mucositis

Mucositis is a common regimen-related toxicity associated with many forms of cancer treatment. Its most obvious manifestation is in the oral cavity where the clinical signs and symptoms are easily recognized. As a result, much of the clinical work in the field of mucositis has concentrated on changes occurring in the oral cavity. Oral mucositis causes a spectrum of clinical symptoms, ranging from mild mucosal erythema to widespread ulceration. The latter is associated with intractable pain that may cause marked disruption of the patient’s quality of life and can compromise their cancer treatment by necessitating drug dose modifications, treatment breaks or even complete treatment cessation. Oral mucositis has been singled out as the worst complication of chemotherapy in conditioning regimens prior to SCT.13 The prevalence of mucositis is variable, depending on the type of treatment given and possibly other factors such as age of the patient and systemic disease. Increasingly, it has been realized that cancer treatment-induced mucosal damage is not confined to the oral cavity and, in fact, extends through the entire length of the alimentary tract (AT), hence the use of the more general term mucosal barrier injury (MBI). This fact is not surprising given the common embryological origin of the majority of the AT. The range of symptoms associated with mucositis or MBI includes not only ulceration and pain, but also gastrointestinal symptoms such as diarrhoea, nausea, malabsorption and malnutrition in association with abdominal pain and bloating. The risk of prolonged hospitalization, the need for increased pain control, serious infection and increased risk of death are associated with the development of mucositis.

What was once thought to be a clinical reflection of epithelial damage is now considered to be a whole mucosal phenomenon arising from a complex interplay between the epithelium and elements within the connective tissue.14 In the last 10 years, the pathobiology of mucositis has been further defined and is now being recognized as an inflammatory complication of antinecancer treatment. The development of mucositis has been divided into five overlapping phases, culminating in tissue damage that manifests clinically as mucositis.15 The five phases are: (i) the initiation phase of free radical generation and induction of apoptotic cell death induced by both DNA and non-DNA damage; (ii) the upregulation and message generation phase in which the master transcription factor, nuclear factor-kappa B (NF-κB), leads to the upregulation of many genes resulting in the production of pro-inflammatory cytokines [tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6]; (iii) the amplification and signalling phase of these pro-inflammatory cytokines; (iv) the net result of ulcerations in the ulceration phase when microorganisms and their cell wall products [peptidoglycan and lipopolysaccharide (LPS)] can cross the damaged physical barrier more easily and are able to activate tissue macrophages to produce more pro-inflammatory cytokines; and (v) the healing phase. Importantly, many of the events that occur in the development of mucositis happen prior to the development of ulceration. Furthermore, it is becoming increasingly apparent that even following resolution of symptoms and healing of ulceration, ongoing alterations in the mucosal structure occur.16

One of the main ‘drivers’ of mucositis is thought to be NF-κB. Human data demonstrated that tissue levels of NF-κB are increased in the buccal mucosa in patients following a variety of chemotherapy regimens for a range of different tumours.17 Further animal studies confirmed that tissue damage occurred throughout the length of the AT, but highlighted that there were differences in the patterns of damage that occurred between the different drugs.18 This highlights the complexity of managing mucositis in the clinical setting where patients are genetically heterogeneous and often given multiple drug combinations. In addition, changes in NF-κB and pro-inflammatory cytokine levels in the serum did not reflect changes in the tissues. The specific reasons for this are unclear, but most likely this is an indication of the global effects of chemotherapy causing widespread alteration of tissues, not just in different mucosal sites.19

Although differences were observed, the ultimate clinical or histological outcome was similar, indicating that the mucosa really has a very limited repertoire in its response to damage; this suggests that there may be a common final pathway leading to the development of mucositis.

Historically, the management of mucositis has been directed at symptom management; however, the development of international guidelines for its management has led to the development of more defined ways of treating this toxicity rather than having a ‘hit and miss’ approach.20 Most recently, the introduction of a recombinant human keratinocyte growth factor, palifermin, to treat mucositis has finally provided an effective treatment to reduce the intensity and chronicity of mucositis in specific clinical situations.21 It is increasingly apparent that toxicities arising from chemotherapy and radiotherapy do not occur in isolation and it has been suggested that there may be common mechanisms relating to the systemic effects of cancer treatment.22 Whilst in the past individual toxicities have been investigated, and often treated, in isolation, this ‘compartmentalization’ may not reflect the true effects of cancer treatment and understanding common pathways may lead to improvement in patient care and better outcomes for patients.
Febrile mucositis

Sonis et al. reported the relationship between the severity of oral mucositis and the incidence of FN and MDI in SCT recipients. The Prospective Oral Mucositis Audit was the first observational study with the duration of severe oral mucositis as the primary endpoint and involved 197 patients with multiple myeloma or non-Hodgkin lymphoma undergoing, respectively, high-dose melphalan or BEAM (BCNU, etoposide, Ara-C, melphalan) chemotherapy and autologous SCT performed at 25 European centres. Patients with severe mucositis had a higher incidence of fever (68% versus 47% of patients; difference 21%; \( P = 0.004 \)), MDI (27% versus 12%; \( P = 0.013 \)) and a longer duration of fever (4.2 versus 3.0 days; \( P = 0.033 \)). Systemic drug exposure was the key determinant of severe mucositis risk. Patients receiving melphalan at doses \( \geq 70 \, \text{mg/m}^2 \) had a 23-fold increased risk of developing mucositis \( (P < 0.001) \) compared with those receiving lower doses. Grazziutti et al. were the first to describe the importance of renal function and variable dose exposure of melphalan in relation to oral mucositis. Even the risk of mortality among SCT recipients suffering from severe oral mucositis is increased. The median time for onset of FN is around day 12 after starting cytotoxic therapy, when mucositis is at its worst. Even more important is the fact that the timing of maximal mucositis correlates independently with the nadir of neutropenia. Fever as a symptom of a systemic inflammatory response measured by C-reactive protein, LPS-binding protein and IL-8 is predominantly driven by the course of mucosal damage measured by mucositis scoring scales, citrulline levels and permeability testing in haematopoietic SCT recipients after myeloablative conditioning. An important observation was that the inflammatory response preceded the bacteraemia by 2 days. This is consistent with a study on rats exposed to chemotherapy, in which the release of pro-inflammatory cytokines was associated with evolving mucositis and preceded microbial translocation. A retrospective analysis of the inflammatory response in 67 uniformly treated SCT patients after high-dose melphalan in our institution clearly indicated that the inflammatory response or fever, in the presence as well as in the absence of bacteraemia, coincided with the occurrence of mucositis and that at least for some SCT recipients, fever is the direct consequence of mucositis alone, irrespective of the duration of neutropenia. Nonetheless, the magnitude of the inflammatory response can be boosted by the onset of bacteraemia. Consequently, the term ‘febrile neutropenia’ may be misleading, as it does not reflect the true nature of fever occurring after cytotoxic therapy and the term ‘febrile mucositis’ may be more appropriate. At present, there are no readily available tools for clinicians to prospectively distinguish febrile mucositis from FN. Although the onset of severe hypocitrullinaemia may turn out to further indicate the high-risk period of bacteraemia, this has to be tested in daily clinical practice. If successful, withholding antimicrobial therapy would be justifiable in cases of febrile mucositis.

I In innate immunity

The normal host defence against pathogenic microorganisms comprises innate and acquired immunity. There are two distinct sets of host responses that are sequentially activated during infection in an attempt to eliminate the pathogen. The innate immune system is activated within minutes after the invasion of the host and is responsible for the defence during the initial hours and days of the infection. A common manifestation of innate immunity involves the induction of inflammatory reactions. Acquired immunity, which comprises cellular and humoral responses, is activated subsequently, following immune recognition of the pathogen. It has been long believed that innate immunity is non-specific. However, this simplistic model, in which innate immunity performs only simple ‘ingest and destroy’ tasks, could not explain how innate immune cells recognize microbial pathogens as ‘non-self’, and why differences are seen between the innate host responses triggered by various classes of microorganisms. It is only during the last decade that it has become clear that the innate immune system not only specifically recognizes various classes of microorganisms, but also initiates and modulates the subsequent adaptive responses delivered by T cells and B cells through their interaction with antigen-presenting cells.

In addition, the dogma of the non-specific nature of the innate immune responses has been challenged by the discovery of novel classes of germ line pattern recognition receptors (PRRs) that sense conserved structures of the invading microorganisms called pathogen-associated molecular patterns (PAMPs). Four major classes of PRRs have been identified, namely toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs) and RiG-I receptors. TLRs are cell membrane-associated (TLR1, TLR2, TLR4, TLR5, TLR6) or intracellular (TLR3, TLR7, TLR8, TLR9) receptors. Among the TLRs, TLR2 recognizes bacterial lipopeptides, TLR3 interacts with double-stranded RNA, TLR4 recognizes LPS and fungal mannans, TLR5 recognizes flagellin, TLR7/8 is important for single-stranded RNA recognition, TLR6 is involved in recognition of zymosan and TLR9 detects fungal DNA. C-type CLRs (CDRs) are mainly membrane-bound receptors that recognize polysaccharide structures: dectin-1 recognizes \( \beta \)-glucans, whereas macrophage mannose receptor and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin recognize fungal mannans and mycobacterial mannosyl-capped lipoparabinomannan, respectively. NLRs are intracellular receptors of bacterial peptidoglycans and danger molecules such as ATP, uric acid or bacterial toxins. RiG-I receptors are intracellular receptors of viral nucleic acids. The blueprint for the structure of these receptors is represented by a pathogen-recognition domain (the leucin-rich repeat domain in TLRs, NLRs and helicases, and the carbohydrate-recognition domain in CLRs) and a signalling domain (TLR-IL1R domain of TLRs, the immunoreceptor tyrosine-based activation-like motif from some CLRs such as dectin-1) that ultimately induce the intracellular signals responsible for the functional activity of the receptor. The interaction of a PRR with a bacterial structure leads to the activation of the host response mechanisms responsible for the elimination of the pathogen: phagocytosis, production of oxygen and nitrogen radicals and especially the release of proinflammatory cytokines responsible for the activation of the phagocytes. Circulating concentrations of proinflammatory cytokines are low or undetectable in healthy individuals, but their production is stimulated during host invasion by pathogenic microorganisms. The main proinflammatory cytokines produced during an infection are TNF-\( \alpha \), IL-1\( \beta \) and IFN-\( \gamma \). They transmit danger signals that alert the
various components of the host defence. Moreover, mucosal and peritoneal lymphocytes secrete higher amounts of cytokines after exposure to chemotherapy. Epithelial cells, especially Paneth cells, possess various PRRs and are an integral component of the anatomical and primary immunological barrier functioning as the frontline of host defence against microorganisms. Damage of the epithelial lining, which has an estimated surface area of 200–300 m² (roughly equivalent to a soccer pitch), is a robust inducer of the systemic inflammatory response after various insults. Downregulation of this inflammatory response by increased secretion of IL-10 seems to have a protective role in restricting excessive mucositis. The PRRs have been also proved to be crucial for bridging the innate and acquired immune responses, by modulating the interaction between dendritic cells and lymphocytes. The progression in our understanding of the mechanisms responsible for pathogen recognition has led to the recognition of several principles for the activation of inflammation during infection, which include: (i) pattern recognition of a pathogen depends on ‘tasting’ of several PAMPs of its cell wall; (ii) despite overlapping and sometimes redundant functions, each ligand/receptor system activates specific intracellular pathways, and this has distinct consequences for the activation of the various arms of the host defence; (iii) differential expression of the various PRRs is an important mechanism for the cell type-specific response; and (iv) the fully integrated response to a specific pathogen depends on the mosaic of PRRs and receptor complexes engaged. The different intracellular events stimulated by these pathways are ultimately responsible for the tailored response of innate immunity to the different types of infections. The insult of chemotherapy appears to jeopardize this delicate balance between host defence and microbial flora, although the true consequences are yet to be elucidated.

Future directions

An intriguing question concerns the role of neutrophils in the pathobiology of mucositis. There is no evidence suggesting that neutrophils play a role in initiating or aggravating mucositis. On the other hand, various studies showed ambivalent results of granulocyte-colony stimulating factor (G-CSF) or granulocyte/macrophage-CSF either given systemically or orally in reducing oral mucositis. However, time to neutrophil engraftment was positively correlated with the duration of severe mucositis. Neutrophil levels in mouth rinses decreased to undetectable levels during the neutropenic period, but recovered 1–2 days after neutrophil counts reached 0.1 and 1.0×10⁹ cells/L, respectively, regardless of whether patients received G-CSF support and marked the beginning of the mucosal recovery phase. Future research should therefore focus on strategies directed at the prevention and treatment of mucositis. Growth factors such as recombinant human IL-11 that protects mucosal barrier integrity of the gut lowered the rate of bacteraemia in patients treated for acute leukæmia. Moreover, palifermin was able to significantly reduce the risk of FN and the rate of severe mucositis in patients undergoing SCT. The importance of recognizing mucositis as an inflammatory complication of cytotoxic therapy will force clinicians to change their approach to directing supportive antimicrobial therapy in those patients developing neutropenic fever.

In addition, in the future, accurate prediction of regimen-related toxicity will be important in improving patient care and quality of life during treatment; whilst there are treatment-related variables that imply a greater risk of mucositis, there is an inherent variability between patients receiving the same treatment. Determining the genetic factors that may increase the risk for toxicity or modulate host defence will ultimately improve treatment outcomes by customizing optimal treatment for individuals.

Transparency declarations

None to declare.

References

Blijlevens et al.


