Chemotherapy induced febrile neutropenia: management and prevention

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Despite recent advances, cytotoxic chemotherapy remains the cornerstone of cancer therapy. In most cases bone marrow suppression represents the dose-limiting toxicity of these drugs. Drug-induced DNA damage at the level of bone marrow progenitor cells results in a fall in circulating neutrophil count. Patients with neutropenia are at increased risk of infection and sepsis.[1] The timing of neutropenia is generally predictable; it typically lasts over a 7–14 day period with the lowest point (nadir) usually around day 10. However, there are exceptions and all patients should be considered to be at risk of sepsis if they have received chemotherapy within the last 28 days. The risk is correlated with both the absolute neutrophil count and the duration of neutropenia: a low nadir (<500/mm^3) and protracted duration (>10 days) are major risk factors for impending infection.[1]

Management of febrile neutropenia

Definitions

- *Fever*: a single oral temperature of 38.3°C or above, or a temperature of 38°C or above for one hour or longer.
- *Neutropenia*: a neutrophil count of 500/mm^3 or less, or a count below 1,000/mm^3 and predicted to fall below 500/mm^3 within 24–48 hours.[2]

In practice, any chemotherapy patient presenting with a sustained fever (≥37.5°C) in the presence of low neutrophil count (<1,000/mm^3) should be treated as potentially septic.

Education and guidelines

All patients undergoing chemotherapy should be educated from the outset concerning the risks and signs and have 24-hour access to emergency telephone triage via the supervising chemotherapy unit. The initial and ongoing management of patients should be co-ordinated by the specialist chemotherapy service provider via triage. In many instances patients will require investigations and management in local secondary care. It is essential to have clear management guidelines available to avoid delays in instigating appropriate management.

Presentation

Symptoms and signs of inflammation are frequently absent in neutropenic patients who typically present with fever in the absence of focal signs. Occult infection is present in 50% of patients who become febrile, although other causes (drugs, disease) should be considered. Approximately 20% of patients with neutrophils below 0.1 × 10^9/l will have bacteraemia[3] with the common bacterial causes listed in Table 1. The primary site of infection is often mucosal damage (mouth or gut) secondary to chemotherapy. The presence of vascular access devices is a further common source. Patients with severe neutropenia or concomitant steroid therapy may present acutely unwell in the absence of fever.

Table 1. Causative organisms in neutropenic fever.

Group	Organism
Gram-positive	Staphylococcus species *Streptococcus pneumoniae* *Streptococcus viridans* *Enterococcus faecalis* Corynebacterium species
Gram-negative	*Escherichia coli* Klebsiella species *Pseudomonas aeruginosa*
Anaerobes	Bacteroides species Clostridium species

Investigations

The onset of fever should trigger early clinical assessment and urgent full blood count with differential. Patients with established neutropenia should undergo immediate blood cultures from a peripheral vein and any intravascular device. Urea, creatinine and electrolytes are important to guide additional supportive care. C-reactive protein levels may guide subsequent management in some instances but the association is not sufficiently consistent to warrant routine clinical use. Routine culture samples from asymptomatic sites (nose, throat etc) are rarely helpful but may provide baseline information on methacillin-resistant *Staphylococcus aureus* colonisation. Chest X-ray should be assessed only in patients with respiratory signs/symptoms.

Treatment

Neutropenia predisposes patients to severe and rapidly progressing infection so empirical broad-spectrum antibiotics should be administered promptly. There are no evidence-based guidelines on timing, but good practice guidelines would support intravenous (iv) antibiotic therapy within 2–4 hours of diagnosis. Afebrile neutropenic patients who have signs and/or symptoms compatible with infection should receive identical management.

Gram-positive organisms increasingly account for most microbiologically documented infections, but initial therapy should consist of broad-spectrum iv therapy because an organism is not identified in the majority of cases.

Despite extensive clinical studies over the last 30 years, no single empirical antibiotic regimen can be recommended. Careful selection based upon local patterns of infection, susceptibility and patient tolerance is advised. In general

terms, monotherapy with a broad-spectrum penicillin (piperacillin/tazobactam), 3rd or 4th generation cephalosporin or penem is reasonable. There is no clear advantage for combination therapy in most uncomplicated episodes of infection,[4,5] but it has some advantages in that it has synergistic effects against some Gram-negative bacilli and there is minimal emergence of drug-resistant strains during treatment.

Glycopeptide therapy (vancomycin) may be important in selected cases with catheter associated infection or mucosal injury,[6] but the emergence of glycopeptide-resistant enterococci should limit its use to specific indications and not as empirical first-line therapy.

Duration of treatment

Antibiotics are normally required for 72 hours to determine efficacy,[2] during which time the clinical course and microbiological results will also guide management (Fig 1). The median clinical response is typically 5–7 days.[2] Where possible, antibiotic modification should be avoided in stable patients, irrespective of fever.

The single most important determinant of successful discontinuation of antibiotics is neutrophil recovery. Patients who are clinically well with no evidence of infection may have their antibiotics stopped after 5–7 days. Those with persistent fever should undergo continuous clinical assessment, with antibiotic modification guided by clinical well-being, culture results and neutrophil recovery. Ongoing discussion with the microbiology department is essential.

Colony stimulating factors (granulocyte colony-stimulating factor (GCSF) and granulocyte-macrophage CSF (GM-CSF)) stimulate neutrophil precursor recovery and can shorten the duration of neutropenia. To date, there is no clear evidence that adding these agents to empirical antibiotics provides significant benefit to the patient or improves cost-effectiveness of management,[7] but CSFs may have a role in complex cases[8] in the presence of protracted neutropenia where the risk of secondary fungal infection is high.

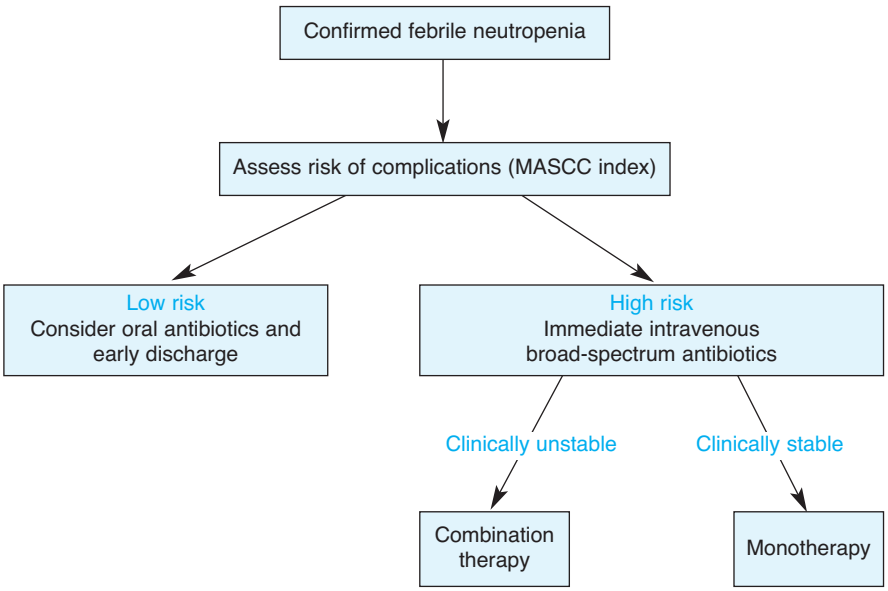

Fig 1. Admission to hospital and management pathway for suspected febrile neutropenia. MASCC = Multinational Association for Supportive Care in Cancer.

Acute leukaemia

The management of leukaemia-related infection poses unique challenges because of the protracted duration and depth of neutropenia. Initial management strategies are identical in all cases, but subsequent care should be managed by specialist units familiar with haematological oncology in close collaboration with microbiology departments.

Risk indices

Although the potential for overwhelming sepsis associated with neutropenia must not be underestimated, only a small proportion of patients presenting with febrile neutropenia (FN) develop serious medical complications. Models have been developed to stratify patients according to their likelihood of developing complications.

Multinational Association for Supportive Care in Cancer risk index

The most established model is the Multinational Association for Supportive Care in Cancer (MASCC) risk index.[9] This uses a weighted scoring system of clinical factors assessed at the time of presentation of FN (Table 2). In practical terms, it has the advantage that it does not require detailed knowledge of

Key Points

- **Consider sepsis in all emergency admissions concerning patients who have received chemotherapy**
- **Request urgent full blood count and differential on all suspected cases of chemotherapy-related infection**
- **Routinely stratify patients according to the Multinational Association for Supportive Care in Cancer risk index**
- **Institute broad-spectrum antibiotics in all confirmed cases**
- **Microbiologically confirmed infections are predominantly Gram-positive**

KEY WORDS: antibiotics, febrile, low risk, neutropenia

Table 2. Multinational Association for Supportive Care of Cancer (MASCC) risk index score.

Characteristic	Score
Burden of illness:*	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status at onset of fever	3
Age <60 years	2

* Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is 26. Patients with an MASCC score index ≥21 are regarded as low risk and <21 high risk.

chemotherapy regimen, the expected timing of nadir, the likely duration of neutropenia or an individual patient's cancer course. It is therefore suitable for use by non-specialist oncology staff.

Newer management approaches in 'low-risk' patients

Prognostic models in FN have been used to identify patients at low risk of developing serious infections and who may be suitable for less intensive, more convenient treatment strategies. These have included oral antibiotics and early hospital discharge/outpatient treatment.

Following two large randomised trials[10,11] which established that oral antibiotics (co-amoxiclav + ciprofloxacin) are equivalent in terms of efficacy and safety to standard parenteral regimens for hospitalised patients with low-risk FN, these oral regimens have been accepted as standard therapy for low-risk patients.[2] Such oral regimens offer the potential for early hospital discharge (after a minimum 24-hour observation period) for low-risk patients with FN.[12,13] However, this represents management at specialist centres. At present, international guidance is that all patients with FN should remain hospitalised until defervescence and neutrophil recovery.

Prevention of infection in chemotherapy-induced neutropenia

Granulocyte colony-stimulating factor

Guidelines produced by both the American Society of Clinical Oncology[8] and the European Organization for the Research and Treatment of Cancer (EORTC)[14] support the routine use of GCSF as primary prophylaxis when treatment is aimed at cure with the risk of FN 20% or above. In this setting, secondary prophylaxis may also be appropriate for patients who have had a previous episode of FN and/or a dose delay due to neutropenia. In the palliative setting, the use of a less myelosuppressive regimen and/or dose/schedule modification is likely to be more appropriate.

Prophylactic antibiotics

The use of prophylactic antibiotics presents an alternative strategy to prevent infection, although this remains a controversial area. Two large trials of prophylactic levofloxacin[15,16] have demonstrated a decrease in the number of febrile episodes and fewer hospital admissions, but no survival benefit was associated with the antibiotic prophylaxis. There is also concern that routine use of antibiotic prophylaxis could lead to the emergence of resistance. Both the EORTC Infectious Diseases Group and the Infectious Diseases Society of America recommend against the routine use of prophylactic antibiotics,[8,14] although they may be appropriate in specific circumstances, for example intensive chemotherapy in preparation for haematopoietic stem cell transplantation.

References

1 Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukaemia. *Ann Intern Med* 1966;64:328–40.

2 Hughes WT, Armstrong D, Bodey GP *et al.* 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.

3 Coullioud D, Van der Auwera P, Viot M, Lasset C. Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients. CEMIC (French-Belgian Study Club of Infectious Diseases in Cancer). *Support Care Cancer* 1993;1: 34–46.

4 Pizzo P, Hathorn JW, Hiemenz J *et al.* A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986;315:552–8.

5 Cometta A, Calandra T, Gaya H *et al.* Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto Infection Programme. *Antimicrob Agents Chemother* 1996;40:1108–15.

6 Cometta A, Kern WV, De Bock R *et al*; International Antimicrobial Therapy Group of the European Organisation for Research and Treatment of Cancer. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis* 2003;37:382–9.

7 Clark OA, Lyman GH, Castro AA *et al.* Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2005;23:4198–214.

8 Smith TJ, Khatcheressian J, Lyman GH *et al.* 2006 update of recommendations for the use of white blood cell growth factors:

an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187–205.
9 Klastersky J, Paesmans M, Rubenstein EB *et al.* The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; 18:3038–51.
10 Freifeld A, Marchigiani D, Walsh T *et al.* A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999;341:305–11.
11 Kern WV, Cometta A, De Bock R *et al.* Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer. *N Engl J Med* 1999;341:312–8.
12 Innes HE, Smith DB, O'Reilly SM *et al.* Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. *Br J Cancer* 2003;89:43–9.
13 Klastersky J, Paesmans M, Georgala A *et al.* Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol* 2006;24:4129–34.
14 Aapro MS, Cameron DA, Pettengell R *et al.* EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;42:2433–53.
15 Bucaneve G, Micozzi A, Menichetti F *et al.* Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 2005;353:977–87.
16 Cullen M, Steven N, Billingham L *et al.* Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med* 2005;353:988–98.

Cancer of unknown primary site

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Cancer of unknown primary site accounts for 3–9% of all patients seen in tertiary cancer centres.[1] The most common sites of presentation (excluding head and neck) are shown in Table 1.[2] The composition of the patient population has changed over the years with the evolution of clinical investigations, the three main aims of which (as with all cancers) are to:

- define the histology
- identify the primary site
- determine the degree of spread.

Identification of the site of origin of the cancer is central to management and understanding of the likely prognosis and treatment possibilities. However, the extent of investigation needs to be tailored to the patient's likely prognosis and prospects for treatment. Exhaustive investigation of poor performance status patients with cancers of unknown primary site is often counterproductive because of the diminishing likelihood of identifying a primary site, the increasing expense of continuing investigation and discomfort to the patient with limited life expectancy.[1,3,4] Even after post-mortem examination the primary site will remain unknown in approximately 15–20%.[5]

Table 1. The most common sites of presentation of cancer where the primary is unknown.[2] Reproduced with permission of the American Cancer Society.

Site of presentation	%
Lymph nodes	30
Bone	15–28
Other abdominal sites	15
Liver	9–31
Lung and pleura	8–12
Central nervous system	8
Skin	8
Adrenal	6

Histology

The histological groups are listed in Table 2.[6]

Adenocarcinoma

The most common histological type is adenocarcinoma, comprising 50–60% of patients in all series. Immunohistochemical tumour markers and molecular genetics allow a more precise diagnosis. A panel of histochemical and genetic markers is increasingly helpful in identifying likely primary sites including:[7-10]

- thyroid transcription factor-1 for lung cancer
- CK7 and CK20 cytokeratins, and CdX to differentiate between gastrointestinal (GI), gynaecological and breast origin
- oestrogen receptor and progesterone receptor for breast and endometrium
- prostate specific antigen (PSA) for prostate.

Table 2. Histological groups of cancers with unknown primary. Data adapted from Reference 6.

Histological group	%
Main malignancies:	
Adenocarcinoma	50–60
Poorly differentiated tumours	35
Squamous carcinoma	5
Other malignancies include:	
Lymphoma	6
Germ cell	1
Melanoma, sarcoma, neuroendocrine	1