OPEN ACCESS

Review Article

Supportive therapy in medical therapy of head and neck tumors

Abstract

Fever during neutropenia may be a symptom of severe life threatening infection, which must be treated immediately with antibiotics. If signs of infection persist, therapy must be modified. Diagnostic measures should not delay treatment. If the risk of febrile neutropenia after chemotherapy is ≥20%, then prophylactic therapy with G-CSF is standard of care. After protocols with a risk of febrile neutropenia of 10–20%, G-CSF is necessary, in patients older than 65 years or with severe comorbidity, open wounds, reduced general condition. Anemia in cancer patients must be diagnosed carefully, even preoperatively. Transfusions of red blood cells are indicated in Hb levels below 7–8 g/dl. Erythropoiesis stimulating agents (ESA) are recommended after chemotherapy only when hemoglobin levels are below 11 g/dl. The Hb-level must not be increased above 12 g/dl. Anemia with functional iron deficiency (transferrin saturation <20%) should be treated with intravenous iron, as oral iron is ineffective being not absorbed. Nausea or emesis following chemotherapy can be classified as minimal, low, moderate and high. The antiemetic prophylaxis should be escalated accordingly. In chemotherapy with low emetogenic potential steroids are sufficient, in the moderate level 5-HT3 receptor antagonists (setrons) are added, and in the highest level Aprepitant as third drug.

Keywords: neutropenia, febrile neutropenia, documented infection, antibiotic therapy, G-CSF, anemia, erythropoiesis stimulating agents, nausea and emesis after chemotherapy, diarrhea

Hartmut Link[1]

1 Klinik für Innere Medizin I, Westpfalz-Klinikum, Kaiserslautern, Germany

Introduction

Infections in neutropenic cancer patients

Neutropenia is a common complication in patients undergoing cytostatic chemotherapy and one of the most important risk factors for infections. Additional factors that contribute markedly to the increased susceptibility to infections include damage to the skin and to the mucous membranes of the oral pharynx and gastrointestinal tract, which can be due to toxic effects of chemotherapy or radiotherapy, or to the neutropenia itself. Fever is often the only indication of infection in neutropenic patients.

While 50% of febrile neutropenic patients have a documented infection initially, infection cannot be localized in the other patients. Even if the infection site cannot be identified, antibiotic therapy must be started immediately to prevent progression to a life-threatening infection. This means that therapy will usually be empirical, based on the results of therapeutic trials and local experience.

Prognostic parameters for infection progression are mainly neutropenia as a surrogate marker and such factors as mucosal damage, severe comorbidity, or antibody deficiency.

Definitions

Neutropenia is defined as a neutrophil count <500/µl, i.e. (segments and bands) or <1000/µl with predicted decline to 500/µl within the next 2 days.

Fever is defined as a temperature taken orally or at the tympanon without any signs of non-infectious causes temperature of ≥38.3°C once or a temperature of ≥38.0°C twice, lasting for at least 1 h or measured twice within 12 h.

Note: Simultaneous infections can be expected in up to 5% of all patients receiving blood transfusions.

Risk groups

Numerous study groups have tried to incorporate further risk-adapted concepts into the decision-making process of empirical therapy. In the case of the so-called low risk group, there are two different concepts: outpatient management and therapy with oral antibiotics. So far, the definitions are not satisfactory, but they can be used for orientation. Apart from general criteria, the low risk definitions that have been used so far include criteria for oral therapy and outpatient management (Table 1). In

Table 1: Risk groups; risk of progression to a life-threatening infection depending on the overall duration of neutropenia

Standard risk with no risk factors	Duration of neutropenia ≤7 days, in the absence of any high risk factor as listed in Table 2
Standard risk with risk factors	Duration of neutropenia ≤7days
High risk	Duration of neutropenia >7 days
Neutropenia	Neutrophil count <500/µl, i.e. (segments and bands) or <1000/µl with predicted decline to 500/µl within the next 2 days

Table 2: Criteria of the low or standard risk group (medical complications considered serious and risk classification according to the "Multinational Association of Supportive Care in Cancer" MASCC [1])

Hypotension: systolic blood pressure less than 90 mmHg or need for pressor support to maintain blood pressure Respiratory failure: arterial oxygen pressure less than 60 mmHg while breathing room air, or need for mechanical ventilation Admission to intensive care Disseminated intravascular coagulation Confusion or altered mental state Congestive heart failure seen on chest x-ray and requiring treatment Bleeding severe enough to require transfusion Arrhythmia or ECG changes requiring treatment Renal failure requiring investigation and/or treatment with IV fluids, dialysis, or any other intervention Other complications judged serious and clinically significant. Microbiologically documented primary viral or microbial infection during the febrile episode, without any described complication and resolving under therapy, was considered a part of the infectious process and was not considered a serious complication.	
A multivariate analysis including many different factors yielded the following risk factors that were weighted in a scoring system that allocates a high number of points to low risk:	
Scoring System	Characteristic Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age, <60 years	2
NOTE: Points attributed to the variable "burden of illness" are not cumulative and the maximum theoretical score is therefore 26. Patients with 21 and more points on this MASCC index can easily be classified into the low risk group. The positive predictive value was 91%, specificity was 68%, and sensitivity was 71%. The commonly used risk criterion "remaining duration of neutropenia" did not correlate well with the actual duration of neutropenia in the present concept and therefore could not be considered.	

non-selected patients approximately 30–40% of all febrile neutropenic episodes can be classified as low risk. The initial classification can be changed during the course of the infection. The state of a patient who initially fails to meet low risk criteria might have stabilized after 12–24 h of therapy, hence outpatient management and oral therapy might be feasible after re-classification. Some investigators never include patients with hematological neoplasia in the low risk group.

The MASCC (Multinational Association for Supportive Care in Cancer) has established a risk index by evaluation of non-selected consecutive patients with febrile neutropenia, according to which low risk patients were defined as defervescing during antibiotic therapy without developing any of the complications listed in Table 2 [1].

Diagnosis

Identification of true pathogens

In approximately one-third of all patients, the causative pathogen can be identified during the initial infection phase. In approximately 20–30% of cases, pathogenic evidence can be found at a later stage. The species listed in Table 3 represent 90% of all proven microorganisms, though fungal infections may initially play a more significant role in pulmonary infiltrates. If pathogens are identified after more than 5 days, fungi can be identified in approximately 30–40% of all microbiologically documented infections.

Table 3: Probable initial pathogenic spectrum upon diagnosis

Frequent	Less frequent
Gram-positive bacteria	
Coagulase-negative staphylococci *Staphylococcus aureus* *Streptococcus spp.* *Enterococcus faecalis/faecium* *Corynebacterium spp.*	*Staphylococcus aureus*
Gram-negative bacteria	
E. coli *Klebsiella* *Pseudomonas aeruginosa*	*Enterobacter* species *Proteus* species *Salmonella* species *Haemophilus influenzae* *Acinetobacter* species *Stenotrophomonas maltophilia* *Citrobacter* species
Anaerobic	
Clostridium difficile	*Bacteroides* species *Clostridium* species *Fusobacterium* species *Propionibacterium* species
Fungi	
Candida spp. *Aspergillus spp.*	*Mucor* species
Pathogens not relevant lung infiltrates, but possibly for simultaneous other infections	
Enterococci from blood cultures, koagulase-negative staphylococci or coryneiform bacilli spp. from all materials, Candida spp., swabs,saliva, sputum, tracheal secretion or brochnoalveolar lavage, surveillance cultures from stools or urine. Other analyses e.g. staphylococcus aureus or legionella from respiratory secretions should be assessed critically for their relevance, before deciding to modify antimicrobial therapy accordingly.	

Infections

Infections in febrile neutropenia can be classified in accordance with the recommendations of the consensus conference of the International Immunocompromised Host Society and the Infectious Diseases Society of America as follows.

Unexplained fever

Unexplained fever or fever of unknown origin (FUO) is defined as a new fever not accompanied by clinical or microbiological evidence of infection: single incident of fever (oral) without any evident cause, temperature ≥38.3°C or ≥38.0°C lasting for at least one hour, or measured twice within 12 hours.

Clinically documented/defined infection

Clinically documented infection (CDI) is defined as fever accompanied by unambiguous, clinically localized evidence, e.g. in the case of pneumonia or skin/tissue infection when pathogens cannot be identified or examined microbiologically.

Microbiologically documented/defined infection with/without bacteremia

A microbiologically documented infection (MDI) is present if the infection has been localized and microbiologically plausible evidence, which is also plausible with regard to timing, has been found, or if an infectious agent can be demonstrated in a blood culture even if a localized infection site has not been identified. koagulase-negative staphylococci and corynebacteria must be demonstrated at least twice in separate blood cultures. A single isolation of these potential pathogens is viewed as contamination. In the case of pulmonary infiltrates, pathogen isolation from blood or a bronchoalveolar lavage specimen is regarded as a reliable source. Throat swabs, sputum, saliva, or a mouth rinse can only be viewed as reliable if a true pathogen is found in a timely correlation with the development of the pulmonary infiltrates. If there are symptoms of abdominal infection, evidence of *Clostridium difficile* toxin from stool culture is acceptable, whereas other potentially pathogenic agents must be found in at least two consecutive stool cultures. In catheter-associated infections, positive blood culture in conjunction with evidence of the same pathogen from the sampled catheter material or a swab taken from the infected entry site is required. For urinary tract infections a significant pathogen count

is necessary; for wound infections, swab or puncture material is acceptable.

Diagnostics – what to do when necessary

Initial clinical diagnostic procedures when an infection is identified

Before initiation of antimicrobial therapy thorough clinical examination covering:

- alterations of skin and mucosa,
- exit sites of central and peripheral venous access routes, puncture sites,
- upper and lower respiratory tract,
- urogenital tract,
- abdomen and perianal region,

(The examination procedures mentioned above should repeated every day if fever persists.)

- monitoring of blood pressure, pulse rate and respiratory frequency.

Further imaging and other diagnostics according to clinical symptoms or risk situation:

- chest x-ray, two views, or high resolution CT-scan of the chest
- other images as indicated in the presence of specific symptoms, e.g.: paranasal sinuses by computed tomography or magnetic resonance tomography,
- abdominal ultrasound, echocardiograpy, retinal examination etc.

Initial microbiological diagnosis

- at least two separate pairs of peripheral venous blood samples for culture (aerobic/anaerobic) taken immediately after rise in temperature, i.e. immediately before initiation of antibiotic therapy. If a venous catheter is in place, two blood cultures should also be taken from the catheter.

Microbiological diagnosis (only if indicated on the basis of infection symptoms)

- Aspergillus Galactomannan – Antigen in serum
- Urine culture
- stool culture including demonstration of clostridium-difficile-enterotoxin in case of diarrhea, suspected enteritis or enterocolitis; if applicable viral diagnostics: Rota-, Noro-virus
- if necessary:
  - wound swab (nasal pharynx, anal region)
  - Liquor: culture for bacteria, fungi; PCR for HSV, if HSV-infection is suspected,
  - puncture material (histology and culture)
  - In the case of positive chest radiography findings bronchoscopy with bronchoalveolar lavage (BAL): Culture and microscopy; if suspected: Cytomegalovirus (CMV), Herpes simplex virus (HSV), Respiratory syncytial virus (RSV), Mycobacteria, Legionellia, Pneumocystis jiroveci, other fungi.
- If a catheter associated indection is suspected: After removal of the venous catheter: Perform a microbiological examination of the catheter tip using a standard technique

Check diagnostics with specialist.
If microorganisms are detected in any culture, a further sample should in any case be taken, even if the treatment is successful, so that a surveillance culture can be established to ensure microbiological effectiveness. Susceptibility testing for medication in use is required for all cultures of potentially pathogenic agents.

Clinical-chemical diagnosis

Minimial diagnostic requirements twice a week before and during therapy:
Leukocytes and differential blood count, hemoglobin, platelets, SGOT, SGPT, LDH, alkaline phosphatase, gamma GT, bilirubin, uric acid, creatinine, sodium, potassium, Quick's test, partial thromboplastin time, D-Dimers, C-reactive protein (CRP); repeated lactate examination if there are signs of sepsis; procalcitonin.
For patients receiving aminoglycosides it is recommended that plasma trough levels be determined at least twice a week or more often if indicated. For patients with renal failure, particularly those simultaneously receiving other potentially nephrotoxic substances, the intervals for plasma level determination should be shortened if aminoglycosides cannot be avoided. It is recommended that creatinine clearance be determined at the outset to guide dosage decisions and evaluate potential nephrotoxicity.

Diagnostic measures after 72–96 hours of therapy without response

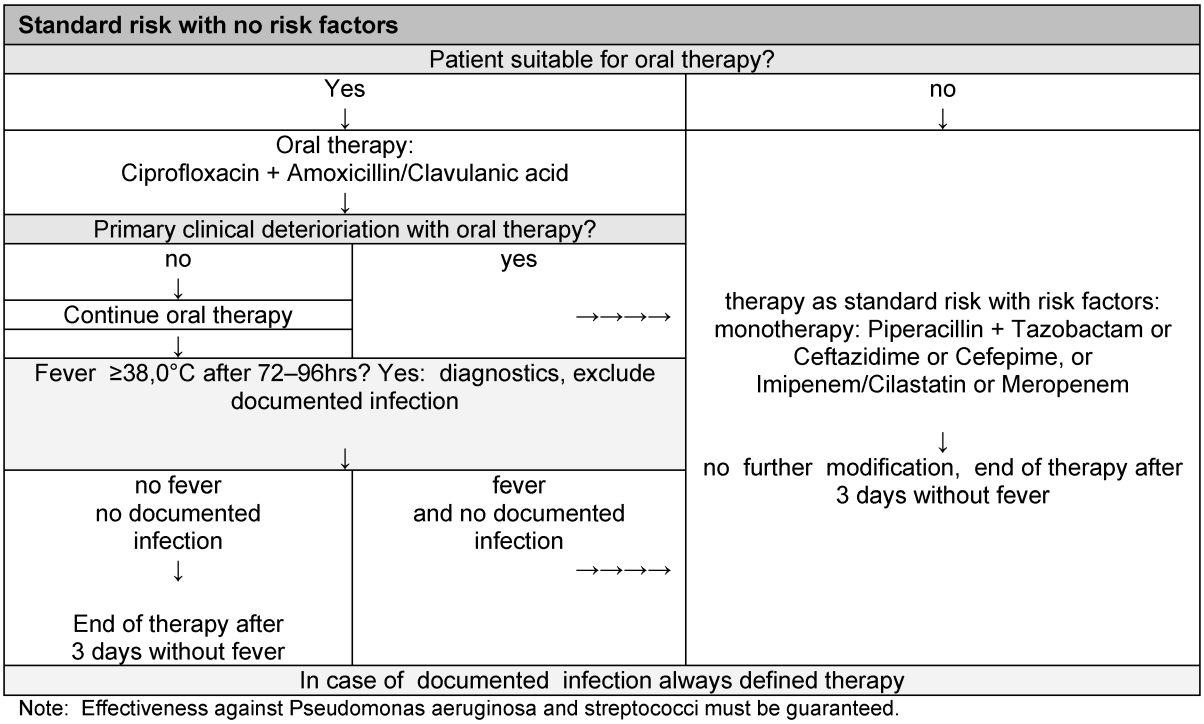
The diagnostic procedures described above should be repeated if radiography of the lungs is still negative and persistent neutropenia: high resolution computed tomography of the lungs abdominal ultrasound.

Therapy strategies

When to start antimicrobial therapy

Prompt initiation of antimicrobial therapy is indicated in the case of

1. Fever and neutropenia <500/µl or <1000/µl if decline to <500/µl is expected
Type of fever: single (oral) temperature of ≥38.3°C or ≥38.0°C lasting for at least one hour or measured twice



Note: Effectiveness against Pseudomonas aeruginosa and streptococci must be guaranteed.

Figure 1

within 12 hours without any evident cause. Exception: fever which is known to be due to non-infectious causes.
or in addition (see separate protocols)

- microbiologically documented infection

or in addition

- clinically or radiologically documented infection

or
2. Signs of infection in afebrile neutropenia

- symptoms or evidence of an infection

or

- clinical diagnosis of septic syndrome or septic shock

Therapy is empiric or calculated, the proof of an infection by a microbial organism cannot be awaited.
Treatment must begin within 2 hours, diagnostic should not delay its initiation.

Therapeutic concepts

Essentially, either combination therapies or monotherapy are possible. Antibiotics chosen should have been adequately investigated and must be effective against enterobacteriaceae, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and streptococci. Monotherapies should only be administered by an experienced team. Patients must be examined regularly and monitored closely for early detection of treatment failure, additional infections, side effects and resistant pathogens.
The hospital- and ward-specific susceptibility patterns of pathogens have to be considered when an antibiotic regimen is chosen. For several years, 60–70% of all documented infections have been caused by gram-positive pathogens, primarily coagulase-negative staphyloccoci and *Corynebacterium jeikeum*. The prognosis of these infections is favourable even if initial therapy was not directed against them, compared to the life-threatening infections by the gram-negative microorganisms *Staphylococcus aureaus*, viridans streptococci and pneumococci.

Classification into risk groups

The classification follows the criteria described in Table 1.

1. standard risk, with no risk factors
2. standard risk with risk factors
3. high risk

Treatment of standard risk patients with no risk factors

Schedule see Figure 1.
For standard risk patients (see Table 1 and Table 2) eligible for oral antibiotic therapy, we recommend the combination of ciprofloxacin plus amoxicillin/clavulanic acid. This combination is also suitable for sequential therapy (possibly only after initial intravenous pre-treatment and stabilization). A high rate of attributable gastrointestinal adverse effects should be taken into account.
Monotherapy with ciprofloxacin or ofloxacin has not been investigated sufficiently. In the case of penicillin allergy, amoxicillin/clavulanic acid can possibly be replaced by clindamycin or cefalexin (little experience) or cefuroximaxetil. For patients with questionable compliance or contraindications for oral therapy, the parenteral medication

Table 4: Antiinfective drugs (alphabetical sorting refer to "Summary of Product Characteristics" (SmPC) and to labelling for different countries!)

Substance	Group*	Dose per day	Route	Notes
Amikacin	AG*	15 mg/kg (maximum 1,5 g daily, maximum 10 Tage)	i.v.	control of serum levels, see below
Amoxicillin/ Clavulansäure	Aminopenicillin/BLI	2 x 1 g	p.o.	
Cefalexin	ceph. gr. 1	2 x 1 g	p.o.	
Cefepim	ceph. gr. 4	2–3 x 2 g	i.v.	
Cefixim	ceph gr. 3	1 x 400 mg or 2 x 200 mg	p.o.	
Ceftazidim	ceph. gr. 3b	3 x 2 g	i.v.	
Cefotaxim	ceph. gr. 3a	3 x 2 g	i.v.	
Cefuroxim-Axetil	ceph. gr. 2	2 x 250 – 2 x 500 mg	p.o.	
Ceftriaxon	ceph. gr. 3a	1 x 2 g	i.v.	
Ciprofloxacin	Chinolon	2 x 0,4 g	i.v.	
		2 x 0,75 g	p.o.	in standard risk patients
Cotrimoxazole (Sulfamethoxazole/ Trimethoprim, fixed combination)	Sulfonamid/ Diaminopyrimidin	Sulfamethoxazole 100 mg/kg; Trimethoprim 20 mg/kg; in 3–4 i.v. Dose; 2–3 weeks	i.v.	In pneumocystis-pneumonia (PcP)
		2 x (Sulfamethoxazole 800 mg; Trimethoprim 160 mg) til 2 x (Sulfamethoxazole 1200; Trimethoprim 240 mg)	p.o. i.v.	normal dosing
Clindamycin	Lincosamid	Moderate severe infections: 1200–1800 mg; severe infections: 2400–2700 mg in 2–4 equal doses	i.v.	
		3 x 600 mg	p.o.	after i.v. therapy
Flucloxacillin	Isoxazolyl-Penicillin	3–4 x 2g	i.v.	
Gentamicin	AG*	3–6 mg/kg	i.v.	serum level controls, see below
Imipenem/Cilastatin	Carbapenem	3 x 1 g or 4 x 0,5 g	i.v.	
Levofloxacin	Chinolon	1 x 0.5 g	i.v. p.o.	
Linezolid	Oxazolidinon	2 x 0,6 g	i.v. p.o.	
Meropenem	Carbapenem	3 x 1 g	i.v.	
Metronidazol	Nitroimidazol	3 x 500 mg	i.v.	
		3 x 400 mg	p.o.	
Mezlocillin	Acylam	3 x 4–5 g or 2 x 10 g	i.v.	
Netilmicin	AG*	4–7,5 mg/kg	i.v.	serum level controls, see below
Piperacillin	Acylam	3–4 x 4 g	i.v.	
Piperacillin/Tazobactam	Acylam/BLI	3–4 x 4,5 g	i.v.	
Teicoplanin	Glykopeptid	1 x 400 mg, 1. Day 2 x 400 mg	i.v.	
Tobramycin	AG*	3–5 mg/kg	i.v.	serum level controls, see below
Vancomycin	Glykopeptid	2 x 1000 mg	i.v.	serum level controls, see below
Vancomycin	Glykopeptid	4 x 125 mg	p.o.	In case of *Cl. diffficile* colitis

*** Target serum concentrations of Aminoglycosides and Vancomycin**

1. First determination: Days 5–7 of therapy, then twice per week together with Creatinine serum level. Earlier determinations might be reasonable if the renal function changes and the dosing must be adapted; especially trough levels and 8h levels correlate with nephrotoxicity
2. Time points: Trough levels just before the next application, 8h-level. 8h after the begin of infusion
3. Dose adaptation: For Aminoglycosides – a dose reduction by 1/3 or 1/2 if the treatment intervals are identical; or prolonging the treatment intervals to 36 or 48 hours

Substance	Peak level (mg/l)	8h-level (mg/l)	troughlevel (mg/l)
Amikacin (single dose)	45–75	2–15	<5
Amikacin q8 h	20–30	–	5–10
Gentamicin (single dose)	4–10	1,5–6	<1
Gentamicin q8 h	4–10	–	<2
Netilmicin (single dose)	15–25	1–5	<1
Netilmicin q8 h	6–10	–	<2
Vancomycin	30–40	–	5–15
Tobramicin (single dose)	4–10	1,5–6	<1
Tobramicin q8 h	4–10	–	<2

* groups of substances: acylam – Acylaminopenicillin, AG – Aminoglykoside, BLI – β-Lactamase-inhibitor, ceph – Cephalosporin and group; antibiotics (dosage in normal renal function)

Table 5: Antimycotics (alphabetical sorting; dosage in normal renal function refer to Summary of Product Characteristics (SmPC) and to labelling for different countries!)

Substance	Group*	Dose per day	Route	Notes
Amphotericin B lipid complex	Polyen, lipid complex	5 mg/kg	i.v.	
Amphotericin B, liposomal	Polyen, liposomes	Start with 3 mg/kg; then dosing according to disease, clinical stage and age of the patient; 1 mg to 3 mg/kg; 3 mg/kg in lung infiltrates; at least 5 mg/kg in zygomycoses	i.v.	
Caspofungin	Echinocandin	70 mg; in patients <80 kg 50 mg from day 2 onwards	i.v.	
Fluconazole	Triazole	400–800 mg	i.v.	
Itraconazole	Triazole	2 x 200 mg Day 1 and 2 i.v., followed by 1 x 200 mg until at least day 5, then oral therapy with suspension 2 x 200 mg possible	i.v. p.o.	oral therapy: trough plasma levels day 5, target value: >500 ng/ml
Posaconazole	Triazole	2 x 400 mg or 4 x 200 mg	p.o.	
Voriconazole	Triazole	i.v.: 1. Day 2 x 6 mg/kg, then 2 x 4 mg/kg; oral: 1. Day 2 x 400 mg/d, then 2 x 200 mg	i.v. p.o.	
Virustatics				
Aciclovir	Nucleosid-Analogon	5–14 days, depending from indication	i.v.	
Ganciclovir	Nucleosid-Analogon	2 x 5 mg/kg, duration according to clinical response	i.v.	

* c.f. Table 4

recommended for intermediate and high risk patients should be used. See Table 4 and Table 5 for dosages.

Treatment of standard risk patients with risk factors and high risk patients

Schedules see Figure 2 and Figure 3, updated from [2], [3], [4], [5].

Strategy for patients with pulmonary infiltrate and possible fungal infection

Pulmonary infiltrate

Antibiotic therapy: piperacillin-tazobactam or ceftazidime or cefepime or imipenem/cilastatin or meropenem combined with antimycotic therapy: liposomal amphotericin B or caspofungin or voriconazole (see also Table 6).

Assessment and duration of therapy

1. initial response: at 72–96 hours after initiation of antimicrobial therapy
2. final response: at the end of antimicrobial therapy
3. after an adequate follow-up period, i.e. 7 days.

Assessment criteria should be based on the recommendations of the consensus conference of the International Immunocompromised Host Society and the Infectious Diseases Society of America [4].

Successful treatment: continuation and follow-up

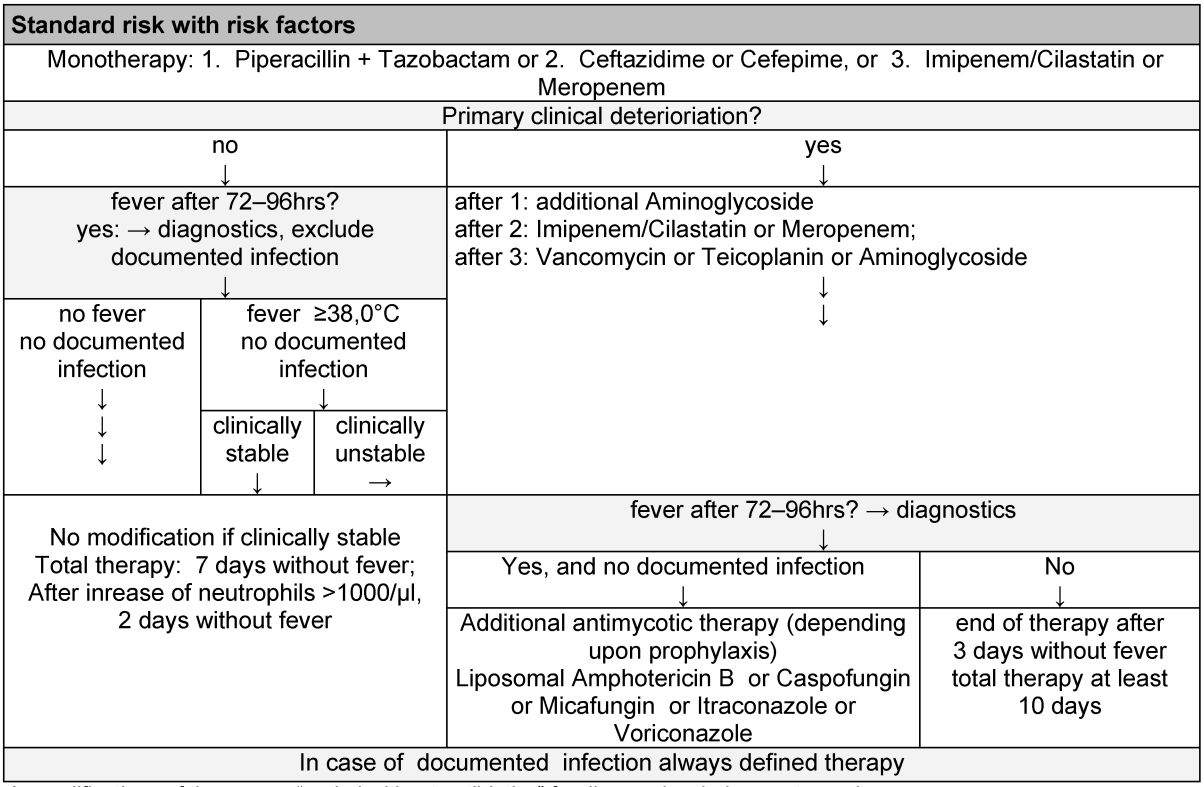
If success criteria are met within 72 hours of antimicrobial treatment and the neutrophil granulocyte count is stable at <1000/µl, the regimen should be continued until the patient is afebrile for seven consecutive days. If, however, the neutrophil granulocyte count has risen to >1000/µl, two consecutive afebrile days are sufficient. Treatment should not be shorter than 7 days. After completion of antimicrobial therapy a follow-up period of 7 days is necessary to detect a relapse or a secondary infection. Some infections only become apparent after an increase in the neutrophil count. Patients with an adequate neutrophil count whose clinical state is improving thus also require follow-up, e.g. on an outpatient basis.

Addional treatment opotions

G-CSF for stimulation of granulopoesis in persistent neutropenia is indicated in case of severe or progressive infection, pneumonia or fungal infection.
In severe hypogammaglobulinemia 7S-polyvalent intravenous immunoglobulins should be substituted.

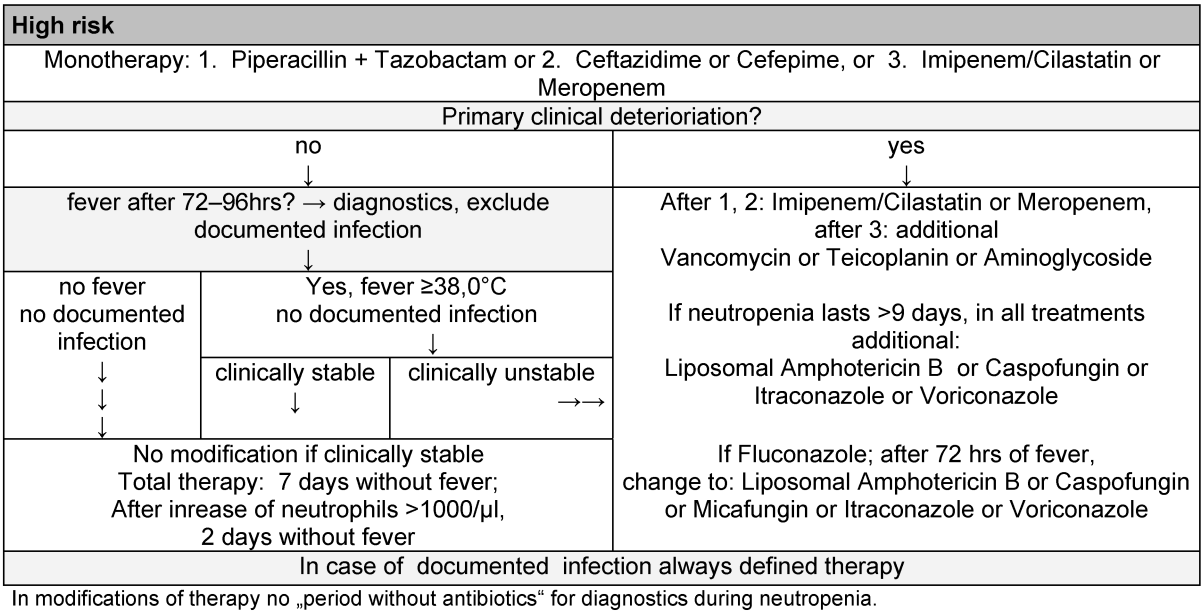
Infection prevention with myeloid growth factors

Many cytotoxic substances impair the function of leukocytes and their production from pluripotent and comitted hematopoietic stem cells in the bone marrow. Frequent sequelae of cytostatic chemotherapy therefore are anemia, thrombocytopenia, leukocytopenia and especially neutropenia, which is a significant risk factor for morbidity and mortality associated with infections. Neutropenia is one of the most severe toxicities of chemotherapy, with its extent and duration being correlated with and increasing risk of serious infections [6], [7], [8]. As most import-



In modifications of therapy no "period without antibiotics" for diagnostics during neutropenia.
Note for azoles: Only if no prophylaxis with azole and no risk of infection with filamentous fungi

Figure 2



In modifications of therapy no „period without antibiotics" for diagnostics during neutropenia.
Note for azoles: Only if no prophylaxis with azole and no risk of infection with filamentous fungi.
Updated from [2, 3, 4, 5]

Figure 3

ant dose limiting toxicity, neutropenia can compromise the success of antineoplastic therapy.

Hematopoietic growth factors such as G-CSF (granulocyte colony stimulating factor) or GM-CSF (granulocyte-macrophage colony stimulating factor) stimulate the generation of neutrophils. G-CSF and GM-CSF are increasingly produced by T-cells, macrophages and monocytes if the neutrophil counts are decreasing, in order to stimulate proliferation and differentiation of comitted progenitor cells. They are termed "myeloid" growth factors.

In the 1980s G-CSF was described, biochemically characterized, its gene cloned and developed as recombinant molecule for clinical application [9], [10]. The prophylactic use of recombinant G-CSF (filgrastim, peg-filgrastim, lenograstim) or GM-CSF preparations (molgramostim, sagramostim) after myelosuppressive chemotherapy ac-

Table 6: Diagnostic and therapeutic strategies (modification or amendment according to symptoms, clinical or microbiological finding in patients with neutropenia and fever)

Finding or symptom	Modification of strategy
Persistent or renewed fever at regeneration of neutrophils or increase of cholestasis	Suspicion of hepatolienal candidiasis: in negative abdominal ultrasound; abdominal CT scan or MRI and decide if antifungal therapy is indicated (see candidemia)
Positive blood culture	
Bevor therapy	
Gram positive bacteria, MSSA MRSA	Flucloxacillin according susceptibility; if necessary Vancomycin, Teicoplanin; Linezolid (antibiogram)
Koagulase-negative staphylococci; *(relevance see diagnostics, Table 3)*	Vancomycin, Teicoplanin
Gram negative bacteria	continue with therapy, if patient stable and pathogen sensitive; if not therapy according to antibiogram
Candida spp.	see below
Pathogen isolated during antibiotic therapy	
Gram positive bacteria	according to antibiogram
Gram negative bacteria	according to antibiogram
Candida spp.	depending from prophylaxis/previous therapy/pathogen/antibiogram (not awaiting result of MHC determination)
a) Fluconazole-sensible +clinically stable + no previous Azol-therapy b) all other cases, especially if *C. krusei* or *C. glabrata*	Fluconazole Caspofungin or Liposomal Amphotericin B or Ampho B-Lipid-complex; in response and regeneration of neutrophils change to Fluconazole or Voriconazole orally, if reasonable by antibiogram, Caspofungin or Voriconazol, if not given initially
Sepsis, septic shock	
	see Figure 2 and Figure 3; or therapy by antibiogram; according usual treatment guidelines of sepsis
Respiratory tract	
Lung infiltrate during recovery of neutrophils	close monitoring, possible inflammatory reaction in neutrophil recovery (n.b. ARDS); directed bronchoalveolar lavage, if not performed yet
Interstitial pneumonia	diagnostics: if induced sputum or bronchoalveolar lavage not possible: suspicion of pneumocystis pneumonia: consider therapy with high dose Trimethoprim-Sulfamethoxazole or Pentamidine; Consider infection by Herpes-Viruses (*herpes simplex*, *cytomegalovirus*) and legionella
Invasive aspergillosis	dependant from previous prophylaxis or therapy: initial therapy: Voriconazole (peferred in CNS-infections); alternatively: Liposomal Amphotericin B secondary: Caspofungin or Liposomal Amphotericin B or Amphotericin B-Lipid-complex or Posaconazole or Voriconazole
Head, eyes, ears, throat	
Necrotizing or borderline gingivitis, paradontitis, necrotizing gingivitis	additional drugs active against anaerobic pathogens (Clindamycine, Metronidazole, Imipenem/Cilastatin or Meropenem)
Vesicles or ulcera	suspicion of h*erpes-simplex*-infection; where appropriate viral cultures; additional empiric Acyclovir therapy
Infiltration of paranasal sinuses or nasal ulcera	suspicion of fungal infection by *aspergillus* spp. or zygomyces, biopsy needed! therapy of aspergillosis (see above) treatment of zygomycosis: high-dose Liposomal Amphotericin B or Amphotericin B Lipid Complex; 5 to 10 mg/kg/d or Posaconazole (if Amphotericin B not possible); local surgery when indicated
Gastrointestinal tract	
Retrosternal pain	suspicion of c*andida* and/or h*erpes-simplex*-infection; bacterial esophagitis possible: consider endoscopy by 48hrs at the latest
	Primary therapy against candida: additional Antimycotics: possibly Fluconazole, Itraconazole or Voriconazole
	if not successful: suspicion of herpes virus infection and therapy with Acyclovir
Acute abdominel pain	suspicion of typhlitis, appendicitis: additional substances active against anaerobe bacteria: Metronidazol, Clindamycin, Imipenem/Cilastatin or Meropenem; close monitoring, possible indication for surgery (!) in case of acute abdomen!
Diarrhea	Suspicion of colitis by *clostridium difficile*: analysis of toxin in stools, Metronidazol orally (in case of need i.v.).; in ineffectiveness: oral Vancomycin
Perianal pain	additional substances active against anaerobe bacteria (see above), frequent and close monitoring, because of possible surgery, especially during regeneration of neutrophils; *herpes-simplex*-virus infection possible as well.

(Continued)

Table 6: Diagnostic and therapeutic strategies (modification or amendment according to symptoms, clinical or microbiological finding in patients with neutropenia and fever)

Finding or symptom	Modification of strategy
Cental venous catheter	
Positive culture for pathogens except of aerobe spore-forming (*Bacillus spp.*) or *Candida spp.*	attempt of i.v. treatment with antibiotics; application via changing of lumen in case of multiple lumina catheter
Staphylococcus aureus (Methicillin/Oxacillin-sensitive)	catheter removal, Isoxazolylpenicillin (Penicillinase-resistant Penicillin) e.g. for example Flucloxacillin, at least 2 weeks
Staphylococcus aureus (Methicillin/Oxacillin-resistent)	catheter removal, therapy according to antibiogram, at least 2 weeks intravenously
Koagulase-negative staphylococci	according to antibiogram; Vancomycin or Teicoplanin only in Methicillin/Oxacillin resistance; duration 5–7 days
Enterococci	Aminopenicillin plus Aminoglycoside; in Ampicillin-resistance: Vancomycin or Teicoplanin plus Aminoglycoside; in Vancomycin resistance: Linezolid; duration of 5–7 days
Coryneform bacteria	according to antibiogram; Vancomycin or Teicoplanin only in resistance against other antibiotics
Positive culture with *Bacillus spp.*	catheter removal, directed therapy
Escherichia coli, klebsiella-species or other *enterobacteriaceae*	according to antibiogram with effective antibiotics: e.g. Cephalosporin group 3, Acylaminopenicillin, Imipenem/Cilastatin or Meropenem, Quinolone antibiotics
Pseudomonas aeruginosa	combination of β-lactam-antibiotic with activity against pseudomonas plus Aminoglycoside, at least 2 weeks
Acinetobacter baumannii	according to antibiogram
Stenotrophomonas maltophilia	according to antibiogram (Cotrimoxazole!)
Candidemia	replace catheter, therapy see above
Clinical infection at exit site	Vancomycin or Teicoplanin
Infection of tunnel or pouch	replace catheter, Vancomycin or Teicoplanin

celerates the regeneration of granulocytes to protective levels [8], [10], [11]. After autologous bone marrow or stem cell transplantation, G-CSF and GM-CSF both accelerate the recovery of granulopoiesis [8], [12], [13], [14]. The prophylactic use of G-CSF is associated with faster neutrophil engraftment and shorter length of post-transplant hospital stay without affecting time to platelet engraftment in patients undergoing autologous transplantation. Following allogeneic stem cell transplantation, G-CSF reduces the time to neutrophil recovery, but has no influence on day 30 or day 100 transplant-related mortality. G-CSF neither affects graft-versus-host disease nor leukemia-free survival [15].

Duration and severity of neutropenia as well as infection-associated risks can significantly be reduced by prophylaxis with myeloid hematopoietic growth factors. that In many cases, hazardous neutropenia can be prevented completely [8], [16], [17]. Meta analyses showed, that infection related mortality and all cause mortality can by reduced by the use of CSFs [17], [18].

Incidence and risks of febrile neutropenia

Febrile neutropenia (FN) is the most important sign of infection in patients after myelosuppressive chemotherapy. FN is defined as an oral temperature ≥38°C along with granulocyte counts <500/µl, or <1000/µl, if a decrease <500/µl within 48 hours is anticipated [3], [19]. Fever during neutropenia is caused by an infection in more than 95% of cases, however in 50–70% of patients no infectious pathogen can be detected [3], [4], [20], [21].

In cancer patients infections are the most frequent therapy-associated causes of death. The risk of febrile neutropenia and of life-threatening infections correlates with the severity and duration of neutropenia [6]. The mortality due to neutropenia-associated infections post-chemotherapy may be up to 5.7%, and is relatively higher when infection occurs early after onset of neutropenia [17], [20], [22], [23].

A multivariate analysis of 41,779 patients with different types of cancer and FN showed the following risk factors for a lethal outcome: Gram-negative sepsis (relative risk: 4.92), invasive aspergillosis 3.48, invasive candidiasis 2.55, pulmonary disease 3.94, cerebrovascular disease 3.26, renal disease 3.16, liver disease 2.89, pneumonia 2.23, gram-positive sepsis 2.29, hypotension 2.12, pulmonary embolism 1.94, heart disease 1.58, leukemia 1.48, lung cancer 1.18, and age ≥65 years 1.12 [23]. An increasing number of concomitant diseases further increases mortality rates [23], [24].

Relative dose intensity of chemotherapy

Relative dose intensity (RDI) is the proportion of planned dose intensity per planned time interval. With the exception of hematopoietic stem cell transplantation, many treatment protocols achieve the planned relative dose intensity only if neutropenia and febrile neutropenia are avoided or limited to a clinically acceptable extent [8]. This is especially true for dose-dense protocols with short

Table 7: Examples of frequently used chemotherapy protocols with the risk of FN: high risk ≥20%, intermediate risk 10–20% or low risk <10% (EORTC guidelines 2010 [39], ASCO-guidelines 2006 [8] and NCCN [19])

Tumor	FN-Risk (%)	Regimen
Breast cancer	>20	AC→Docetaxel; Doxorubicin/Docetaxel; Doxorubicin/Paclitaxel; TAC DDG (does dense regimens, supported by primary prophylaxis with G-CSF)
	10–20	AC; EC; Docetaxel; FEC-100; CEF
	<10	CMF
Colorectal cancer	10–20	5-FU/Folinic acid FOLFIRI (5-FU/Folinic acid/Irinotecan)
	<10	FOLFOX (5-FU/Folinic acid/Oxaliplatin)
Gastric cancer, metastatic	>20	DCF, TC, TCF, ECF, LV-FU-Cisplatin
	10–20	Docetaxel-Irinotecan, Folfox-6
Hodgkin's lymphoma	>20	BEACOPP: Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Voncristine, Procarbazine, Prednisone
Melanoma	>20	Dacarbacine based combinations
Non small cell lung cancer	>20	Docetaxel/Carboplatin; Etoposid/Cisplatin; Cisplatin/Vinorelbin/Cetuximab
	10–20	Paclitaxel/Cisplatin; Docetaxel/Cisplatin; Vinorelbin/Cisplatin
	<10	Paclitaxel/Carboplatin; Gemcitabine/Cisplatin
Non-Hodgkin-Lymphoma	>20	CHOP (Cyclophosphamide/Doxorubicin/Vincristin/Prednison) DHAP (Cisplatin, HD-AraC, Dexamethason) ESHAP (Etoposide, Methylprednisolone, Cisplatin, Cytarabine) R-CHOP (Rituximab-CHOP)
Prostate cancer	10–20	Cabacitaxel
Ovarian carcinoma	>20	Docetaxel; Paclitaxel
	10–20	Topotecan
	<10	Paclitaxel/Carboplatin
Small cell lung cancer	>20	ACE, ICE, Topotecan,
	10–20	Etoposid/Carboplatin; Topotecan/Cisplatin
	<10	Paclitaxel/Carboplatin

A: Doxorubicin, C: Cyclophosphamide, E: Etoposide, F: 5-Fluorouracil, I: Ifosfamide, M: Methotrexate, T: Docetaxel
All figures of febrile neutropenia are derived from the original publications and are related to the dosages of the applied chemotherapy protocols.
Refer to guidelines of original publications for incidences of febrile neutropenia for details and if other protocols are considered.

intervals between cycles and increased dose intensities, for example in Hodgkin's lymphoma [25], aggressive Non-Hodgkin's lymphoma [26], [27], [28], and breast cancer [29].

Reduction of relative dose intensity of chemotherapy

It is a common strategy to reduce the dose of chemotherapy in subsequent cycles or prolonging intervals between treatment cycles, when severe or febrile neutropenia have occurred after a preceding course. Randomized clinical trials in adult solid tumor and malignant lymphoma patients showed a relative dose intensity (RDI) of 71.0% to 95.0%, with a mean RDI of 86.7% (median RDI, 88.5%). Among G-CSF–treated patients, the average RDI ranged from 91.0% to 99.0%, with a mean RDI of 95.1% (median RDI, 95.5%). RDI differences between study arms ranged from 2.8% to 20.0%, with average differences of 8.4% (*P*=.001) [17].

In some tumors it has been shown that reducing the RDI can have a negative impact on the success of chemotherapy, e.g., in adjuvant chemotherapy for breast cancer [30], [31], [32], [33], in diffuse large cell Non-Hodgkin's lymphoma [34].

In Non-small-cell lung cancer it has been clearly shown, that patients >56 years have a siginificant longer survival, if they receive a combination chemotherapy as compared with a single agent therapy [35].

Risk factors for febrile neutropenia

The most important factors for febrile neutropenia (FN) following chemotherapy are the type of chemotherapy and its dose intensity. Without G-CSF or GM-CSF, the risk of FN is constant for all chemotherapy cycles [36], [37]. However, it is greater following the first cycle only, if hematopoietic growth factors are given for subsequent cycles [38]. If neutropenic complications occur, then the risk of febrile neutropenia remains high for further chemotherapy cycles.

Combination chemotherapy protocols increase the risk of FN compared to monotherapies, as well as drugs toxic to bone marrow or mucous membranes. Significant predictors for severe or febrile neutropenia are the use of high-dose cyclophosphamide or etoposide for treatment of malignant lymphomas as well as high-dose antracyclines for early breast cancer [19].

According to various guidelines, the intensity of chemotherapy protocol correlates directly with the risk of FN. An overview on frequently used protocols is given in Table 7, with the risk of FN categorized as high (≥20%), intermediate (10–20%) or low (<10%) [39].

Table 8: Risk factors of febrile neutropenia according National Comprehensive Cancer Network, NCCN 2010) [19], EORTC [16] and ASCO [8]

Chemotherapy related factors
• Type of chemotherapy
• Severe neutropenia with previous comparable chemotherapy
• >80% of planned relative dose intensity
• Previous neutropenia (<1000/µl) or lymphocytopenia
• Previous extensive chemotherapy
• Concomitant or previous radiotherapy with involvement of bone marrow
• Therapy with anthracyclines
• Mucositis of the whole gastrointestinal tract
Patient risk factors
• Age 65 years or older
• Female gender
• Poor performance status (ECOG ≥2 "Eastern Cooperative Oncology Group")
• Poor nutritional status
• Impaired immune function
Tumor risk factors
• Cytopenias due to tumor bone marrow involvement
• Advanced or uncontrolled tumor
• Elevated lactate dehydrogenase (LDH) in lymphoma
• Leukemia
• Lymphoma
• Lung carcinoma
Factors with increased risk for infections
• Open wounds
• Active infection
Comorbidity
• chronic obstructive lung disease
• cardiovascular disorder
• Liver disease (elevated bilirubin, alkaline phosphatase)
• Diabetes mellitus
• Decreased hemoglobin level at diagnosis

Besides the type of chemotherapy, patient- and tumor-specific factors have an impact on the risk of febrile neutropenia (Table 8).

A review of the literature showed that higher age, especially ≥65 years, consistently correlates with a higher risk of febrile neutropenia among independent patient-specific risk factors [16]. In elderly patients, chemotherapy may be underdosed in fear of neutropenic complications, although they would benefit from conventional-dose treatment regimen as younger patients do [19].

Apart from higher age, independent risk factors for febrile complications during neutropenia are advanced disease, previous episodes of FN and lacking prophylaxis with G-CSF or antibiotics [16]. Other patient- or tumor-related risk factors for FN, such as reduced general condition, impaired nutritional status or comorbidity, have been identified with a lower level of evidence by retrospective analyses. Patients with malignant diseases of hematopoiesis or lymphopoiesis have an increased risk by the disease itself and the intensity of the treatment than patients with solid tumors.

In the group of patients older than 70 years, increasing age does not increase the risk of severe or febrile neutropenia further, but the type of the malignancy, a planned dose intensity ≥85%, therapy with cisplatinum or anthracyclines, previous chemotherapy, increased urea and increased alkaline phosphatase [40].

Indication for G-CSF prophylaxis according to guidelines

Most data on clinical efficacy of recombinant myeloid growth factors is derived from studies using G-CSF. The principle of reducing neutropenia with myeloid growth factors is shown in Figure 4. Neutropenia can be shortened mainly by an accelerated recovery of neutrophils.

Primary prophylaxis with G-CSF reduces by half the incidence of febrile neutropenia (FN) after chemotherapy associated with a risk of FN of at least 40% [11], [41], [42], [43].

Primary G-CSF prophylaxis in patients receiving cancer chemotherapy is recommended for all patients with an expected ≥20% risk of FN [8], [16], [19], [39]. If using a chemotherapy regimen associated with 10%–20% FN risk, G-CSF prophylaxis should be considered based on treatment intention and individual patient risk factors. The patient's FN risk should be reassessed prior to each cycle of chemotherapy. This is particularly important for chemotherapy regimens with 10%–20% FN risk, as patient-related risk factors may vary throughout chemotherapy cycles, and thus their FN risk could increase throughout the treatment course. For patients at <10% FN risk, G-CSF prophylaxis generally is not recommended.

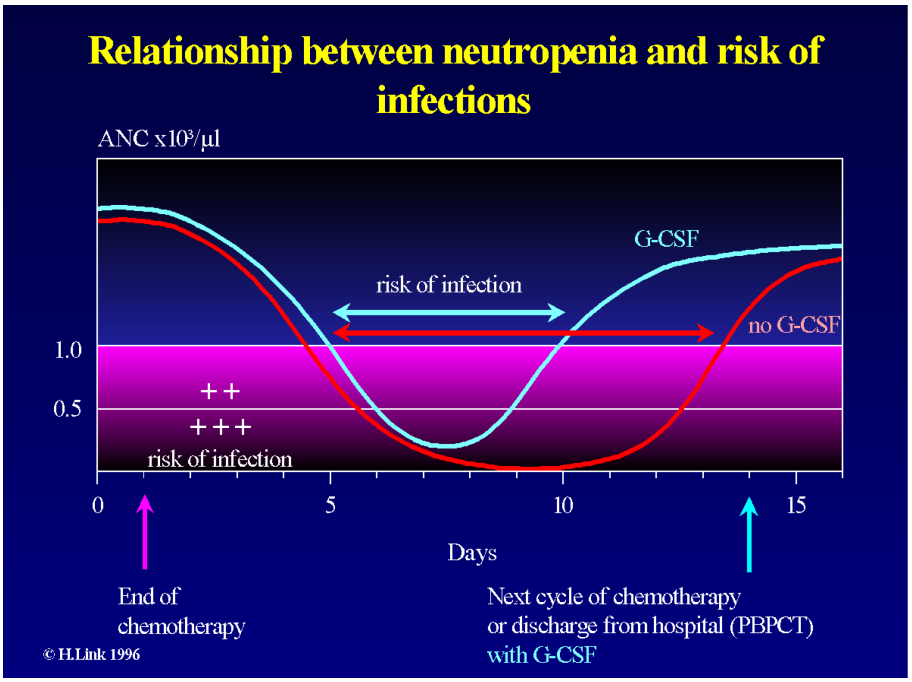


Figure 4: Correlation between incidence of infections including febrile neutropenia and neutrophil recovery

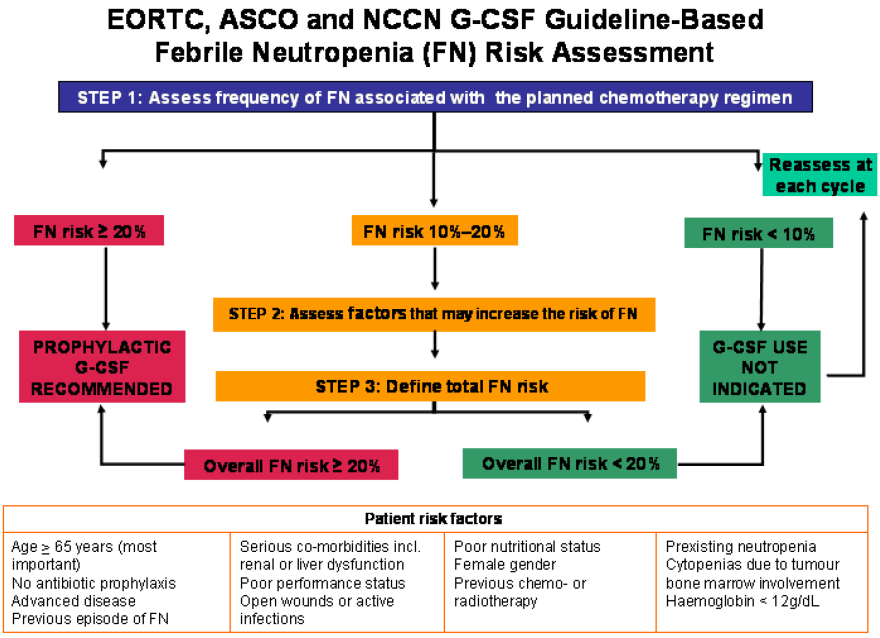


Figure 5: This algorithm is a combined interpretation of the 2010 G-CSF guidelines of European Organisation for Research and Treatment of Cancer (EORTC) and American Society of Clinical Oncology (ASCO) [8, 39]. All of these organisations recommend that the physician should use their clinical judgement to assess FN risk as greater or less than 20% according to the estimated risk of expected neutropenic complications, based on the treatment regimen and patient-specific characteristics, including age ≥65 years and experience of FN in a previous chemotherapy cycle.

Prophylactic antibiotics are not advised in standard risk patients with an anticipated risk of neutropenia for <7 days [19], [39], [44]. Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC <100 cells/µl for >7 days) [44].
Figure 5 shows the algorithm for deciding to use G-CSF after chemotherapy.

Therapeutic use of G-CSF or GM-CSF in patients with existing febrile neutropenia

The aim of therapeutic use of myeloid growth factors is the reduction of morbidity and mortality due to infections emerging during neutropenia. In patients with solid tumors and high risk FN, therapeutic G-CSF in addition to antibiotic therapy was beneficial by reducing the duration of neutropenia and hospitalisation with significantly less

serious medical complications [45]. However, there is less evidence supporting the therapeutic use of G- or GM-CSF in addition to antibiotics. A meta-analysis showed a shorter hospital stay and shorter time to neutrophil recovery, but no influence on mortality [46]. Interventional application of recombinant myeloid growth factors can be considered for patients with risk factors for poor clinical outcome or infection-related complications such as age ≥65 years, sepsis syndrome, severe neutropenia with an absolute neutrophil count <100µl, anticipated duration of >10 days of severe neutropenia, pneumonia, or invasive fungal infections [19].
Patients under prophylaxis with G-CSF, who develop febrile neutropenia, should continue this prophylaxis.

Dosing and administration

Available growth factors are the G-CSFs filgrastim, pegfilgrastim, lenograstim and the GM-CSFs sargramostim, molgramostim. Primary prophylaxis should be given beginning with the first cycle of chemotherapy in solid tumors and non-myeloid malignancies until post nadir recovery of neutrophils [19]. Administration of CSFs on same of chemotherapy is not recommended [19]. Alternative dosing schedules are not recommended [19].

G-CSF

G-CSF should be given 24–72 hrs following the last dose of chemotherapy and continued until the recovery of neutrophils for three days above 500 cells/µl or until reaching an ANC of at least 2,000 to 3,000/µl.
Filgrastim is given subcutaneously (s.c.) at a dose of 5 µg/kg per day, lenograstim at 150µg/m^2 per day.
The long acting pegylated G-CSF (pegfilgrastim) is given s.c. once at a dose of 6 mg 24 hours after completion of each cycle of chemotherapy. The 6 mg formulation should not be used in infants, children, or small adolescents weighing <45 kg.

GM-CSF

The GM-CSF sargramostim (glycosylated), which is not available on the market in many countries, is licensed for prophylactic use following chemotherapy in patients with acute myeloid leukemia, or after autologous or allogeneic bone marrow transplantation. The manufacturer's instructions for administration are limited to those clinical settings. GM-CSF should be initiated on the day of bone marrow transfusion, not less than 24 hours from the last chemotherapy and not earlier than 12 hours from the most recent radiotherapy. GM-CSF should be continued until an ANC greater than 1,500 cells/µl for 3 consecutive days is obtained. The drug should be discontinued early or the dose be reduced by 50% if the ANC increases to greater than 20,000 µl. The recommended doses are 250 micrograms/m^2/day for GM-CSF for all clinical settings, given subcutaneously.

The GM-CSF molgramostim (non-glycosylated) is licensed for use in patients receiving myelosuppressive therapy (cancer chemotherapy) to reduce the severity of neutropenia, thereby reducing the risk of infection and allowing better adherence to the chemotherapeutic regimen, in patients undergoing autologous or syngeneic bone marrow transplantation to accelerate myeloid recovery. Recommended dosage regimens are for cancer chemotherapy 5 to 10 µg/kg per day administered subcutaneously, initiated 24 hours after the last dose of chemotherapy and continued for 7 to 10 days, And after bone marrow transplantation 10 µg/kg per day administered by i.v. infusion over 4 to 6 hours, beginning the day after BMT, and continued until the absolute neutrophil count (ANC) reaches ≥1000/µl. The maximum duration of treatment is 30 days.
Several studies suggest, that the application of the long lasting Pegfilgrastim provides an optimal dosing of G-CSF and might thus be more effective than the daily injected G-CSF, which some patients might receive in suboptimal daily schedules [39]. One metaanalysis comparing pegfilgrastim with filgrastim found a significant lower rate of febrile neutropenia with Pegfilgrastim [18].

Anemia in cancer

Anemia causing clinical symptom is characterized as a decline of hemoglobin below 12 g/dl. Initially, the incidence is about 50% or more, depending on the type and stage of cancer [47].
Following anemia due to iron deficiency, the anemia of chronic disease is the second most form, which is caused by the activated immune system [48].
An anemia should be evaluated and treated accordingly, see Table 9.

Laboratory findings in anemia of chronic disease (ACD)

ACD is chracterized by normochromic or hypochromic, microcytic erythrocytes (MCV, MCH normal or slightly decreased), anisocytosis, poikilocytosis. The reticulocyte count can be normal or decreased.
Reticulocyte hemoglobin (CHr) <26 pg, or al level of >10% hypochomic erythrocytes is typical.
Ferritin levels are elevated due to inflammation, the transferrin saturation is low.
The Erythropoietin serum levels are higher than at normal hemopglobin levels, but not sufficiently increased [49].

Treatment of anemia

The indication for blood transfusions has to be assessed if the hemoglobin level is below 8g/dl and the patients has symptoms of anemia. The German Board of Physicians recommends transfusions in chronic anemia only, if the hemoglobin level is below 7–8 g/dl [50]. Only if

Table 9: Diagnostics in suspected anemia ov chronic disease (ACD), exclusion of additional causes of anemia

Iron deficiency
Blood loss
Difeciency of Vitamin B12 (Cobolamin)- or folic acid
Hemolysis
Renal insufficiency
Hematological disorder
Laboratory diagnostics
Blood count with MCV, MCH , quantitative reticulocyte count
Differential blood count
Routine test with liver, kidney parameters:
Iron status: Ferritin, transferrin, transferrin saturation
hypochrome erythrocytes
Retikulocyte hemoglobin (CHr)
Holo-Trans-Cobalamin (Vitamin B12), folic acid
Tests for inflammation: ESR, Fibrinogen, CRP, Haptoglobin, LDH
in certain cases: Erythropoietin concentration
Test of stools for occult blood

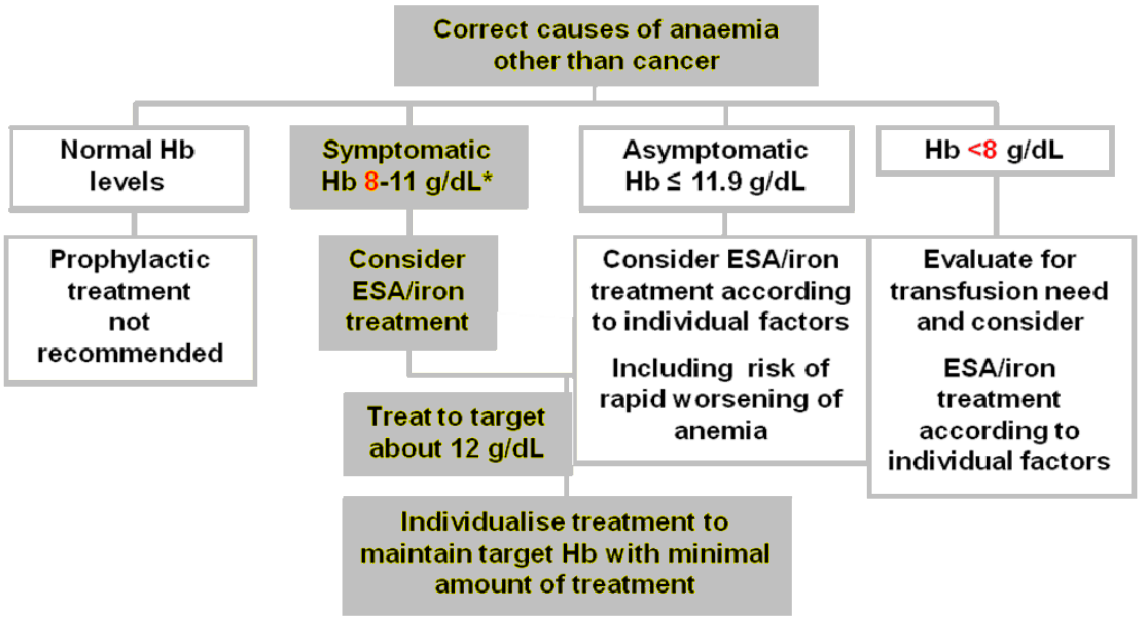


Figure 6: EORTC Guidelines for Erythropoietic Proteins in Anaemic Patients with Cancer Chemotherapy: 2011 Update

patients do not tolerate that level, then transfusions can be given at higher hb-levels.
However, the risks of blood transfusions should be considered, such as infections, intolerance, sensitizing, higher mortality, secondary malignant lymphomas, and higher risk of tumor relapse [51], [52], [53], [54], [55].

Specific therapy of anemia

a) Iron deficiency due to bleeding or nutritional deficiency, no inflammation, no active tumor.
a1) Oral iron substituion: 100 mg/d Fe(II) sulfate or other Fe(II) compound.
a2) Intravenous iron substitution, in intolerance or ineffectiveness of oral preparations.
b) Iron deficiency in anemia of chronic diesease (ACD) in inflammation or tumor, functional iron deficiency; combination of i.v. iron with erythropoietic agents (ESA).
In anemia following chemotherapy, Hb levels ≤11 g/dl, and therapy with ESA, it is recommended to regularly measure the iron parameters [56] and to substitute with intravenous (iv) iron [57].
c) In ACD without chemotherapy only i.v. iron or blood transfusions (if hb<8 g/dl) are recommended.
d) Anemia following chemotherapy: Therapy with ESA if the patients is symptomatic and the hemoglobin is ≤11 g/dl [56], [57], see Figure 6.
ESAs are not approved in anemic patients with radiotherapy.

Chemotherapy induced nausea and vomiting

Chemotherapy can induce nausea and vomiting, which are among the most important side effects. However ac-

Table 10: Emetogenic potential of intravenously applicable antineoplastic substances; selected drugs, which are in use for head and neck tumors

High	**emetic risk without antiemetic prophylaxis >90%**	
Carmustine, BCNU		Cyclophosphamide (>1500 mg/m²)
Cis-Platinum		
Moderate	**emetic risk without antiemetic prophylaxis 30–90%**	
Cyclophosphamide (<1500 mg/m²)		Epirubicin
Daunorubicin*		Ifosfamide
Doxorubicin*		Irinotecan
Low	**emetic risk without antiemetic prophylaxis 10–30%**	
Cetuximab		Paclitaxel
Docetaxel		Panitumumab
Etoposide i.v		Pemetrexed
5-Fluorouracil		Teniposide
Gemcitabine		Thiopeta
Methotrexate (>100 mg/m²)		Topotecan
Minimal	**emetic risk without antiemetic prophylaxis <10%**	
Bleomycine		Vinblastine
Bevacizumab		Vincristine
Methotrexate (<100 mg/m²)		Vinorelbine

The cytostatic with the highest risk defines the risk group. The addition of further drugs in combination chemotherapy protocols does not increase the risk further. However some anthracyclines, marked by asterisks (*) are considered as high risk in combination with cyclophosphamide.

Table 11: Emetogenic potential of orally applicable antineoplastic substances

Moderate	**emetic risk without antiemetic prophylaxis 30–90%**	
Cyclophosphamide		Vinorelbine
Low	**emetic risk without antiemetic prophylaxis 10–30%**	
Capecitabin		Etoposide
Minimal	**emetic risk without antiemetic prophylaxis <10%**	
Erlotinib		Methotrexate
Gefitinib		

tual standard therapy can prevent vomiting in almost all patients. Nausea still being a major subjective problem. Preventing nausea and vomiting is an essential supportive measure in oncology.

Medical treatment

In order to avoid anticipatory vomiting, it is necessary to apply the antiemetic medication as prophylaxis during tumor therapy. The American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC) have published guidelines for prevention and control of nausea and vomiting, which are summarized in the following [58], [59].

In principle the antiemetic therapy is oriented along the emetic potential of cytostatics, see Table 10 and Table 11.
Table 12 summarizes the recommendations for antiemetic prophylaxis.

Notes

Competing interests

The author has received lectureship honoraria from Amgen, Janssen, Hexal/Sandoz, Teva, Vifor-Pharma; research funding from Amgen and consultancy honoraria from Amgen, Teva, Vifor-Pharma.

Table 12: Antiemetic prophylaxis in chemotherapy on day 1 (acute phase) and days 2–4 (delayed phase), according ASCO- and MASCC-Guidelines [58, 59]

Emetogenic potential	Acute Phase, until 24 h after chemotherapy, day 1	delayed Phase, after 24 h (day 2) until day 3 (4) after chemotherapy
High	Combination of 3 substances: 1. 5-HT_3-Receptor-antagonist: a) Granisetron 2 mg p.o./1 mg i.v. b) Ondansetron 16 mg p.o./8 mg i.v. c) Tropisetron 5 mg p.o./i.v. d) Palonosetron 500 µg p.o./ 0,25 mg i.v. + 2. Steroid: Dexamethason 12 mg p.o/i.v. + 3. Neurokinin-1-Receptor-antagonist: Aprepitant 125 mg p.o. or Fosaprepitant 115 mg i.v. (not applicable days 2 und 3)	Combination of 2 substances (no 5-HT_3 Receptor-antagonist): 1. Steroid: Dexamethason 8 mg p.o./i.v. days 2 und 3 (if necessary also day 4) + 2. Neurokinin-1-Receptor-antagonist: Aprepitant 80 mg p.o. for days 2 and 3 (not applicable if fosaprepitant i.v. on day 1)
Moderate	Combination of 2 substances: 1. 5-HT_3- Receptor-antagonist (dosages s.o.) a) Palonosetron (preferred) b) Granisetron c) Tropisetron + 2. Steroid: Dexamethason 8 mg p.o/i.v.	Steroid: Dexamethason, 8 mg p.o /i.v. for days 2 and 3
	There is only limited experience for the additional use of Aprepitant in moderate emetogenic chemotherapy; if a 3 drug combination is chosen, then any 5-HT3-Receptor-antagonist is suitable.	
Low	Steroid: Dexamethason 8 mg p.o/i.v.	No routine prophylaxis
Minimal	No routine prophylaxis	No routine prophylaxis

References

1. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K, Talcott J. 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 Aug;18(16):3038-51.
2. Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO); Böhme A, Ruhnke M, Buchheidt D, Cornely OA, Einsele H, Enzensberger R, Hebart H, Heinz W, Junghanss C, Karthaus M, Krüger W, Krug U, Kubin T, Penack O, Reichert D, Reuter S, Silling G, Südhoff T, Ullmann AJ, Maschmeyer G. Treatment of invasive fungal infections in cancer patients – "Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)". Ann Hematol. 2009 Feb 1;88:97-110. DOI: 10.1007/s00277-008-0622-5
3. Link H, Böhme A, Cornely OA, Höffken K, Kellner O, Kern WV, Mahlberg R, Maschmeyer G, Nowrousian MR, Ostermann H, Ruhnke M, Sezer O, Schiel X, Wilhelm M, Auner HW; Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO); Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). Antimicrobial therapy of unexplained fever in neutropenic patients – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). Ann Hematol. 2003 Oct;82(Suppl 2):S105-17. DOI: 10.1007/s00277-003-0764-4
4. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002 Mar 15;34(6):730-51. DOI: 10.1086/339215
5. Maschmeyer G, Beinert T, Buchheidt D, Cornely OA, Einsele H, Heinz W, Heussel CP, Kahl C, Kiehl M, Lorenz J, Hof H, Mattiuzzi G. Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: Guidelines of the infectious diseases working party of the German Society of Haematology and Oncology. Eur J Cancer. 2009 Sep;45(14):2462-72. DOI: 10.1016/j.ejca.2009.05.001

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

7. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004 Jan 15;100:228-37. DOI: 10.1002/cncr.11882

8. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2006 Jul 1;24:3187-205. DOI: 10.1200/JCO.2006.06.4451

9. Welte K, Platzer E, Lu L, Gabrilove JL, Levi E, Mertelsmann R, Moore MA. Purification and biochemical characterization of human pluripotent hematopoietic colony-stimulating factor. Proc Natl Acad Sci USA. 1985 Mar;82(5):1526-30.

10. Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): The first 10 years. Blood. 1996;88(6):1907-29.

11. Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, Kris M, Grous J, Picozzi V, Rausch G, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med. 1991;325(3):164-70. DOI: 10.1056/NEJM199107183250305

12. Link H, Boogaerts MA, Carella AM, Ferrant A, Gadner H, Gorin NC, Harabacz I, Harousseau JL, Hervé P, Holldack J, et al. A controlled trial of recombinant human granulocyte-macrophage colony stimulating factor after total body irradiation, high dose chemotherapy and autologous bone marrow transplantation for acute lymphoblastic leukemia or malignant lymphoma. Blood. 1992;80:2188-95.

13. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, Demuynck HM, Link H, Zander A, Barge A. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet. 1996;347:353-7. DOI: 10.1016/S0140-6736(96)90536-X

14. Dekker A, Bulley S, Beyene J, Dupuis LL, Doyle JJ, Sung L. Meta-Analysis of Randomized Controlled Trials of Prophylactic Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor After Autologous and Allogeneic Stem Cell Transplantation. J Clin Oncol. 2006 Nov 20;24:5207-15. DOI: 10.1200/JCO.2006.06.1663

15. Khoury HJ, Loberiza FR Jr, Ringdén O, Barrett AJ, Bolwell BJ, Cahn JY, Champlin RE, Gale RP, Hale GA, Urbano-Ispizua A, Martino R, McCarthy PL, Tiberghien P, Verdonck LF, Horowitz MM. Impact of posttransplantation G-CSF on outcomes of allogeneic hematopoietic stem cell transplantation. Blood. 2006 Feb 15;107(4):1712-6. DOI: 10.1182/blood-2005-07-2661

16. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, Kearney N, Lyman GH, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party. 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. DOI: 10.1016/j.ejca.2006.05.002

17. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of Primary Prophylaxis With Granulocyte Colony-Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: A Systematic Review. J Clin Oncol. 2007 Jul 20;25:3158-67. DOI: 10.1200/JCO.2006.08.8823

18. Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2007 Aug 10;23:2283-95. DOI: 10.1185/030079907X219599

19. Crawford J, Allen J, Armitage J, Blayney DW, Cataland SR, Heaney ML, Htoy S, Hudock S, Kloth DD, Kuter DJ, Lyman GH, McMahon B, Steensma DP, Vadhan-Raj S, Westervelt P, Westmoreland M; National Comprehensive Cancer Network. Myeloid growth factors. J Natl Compr Canc Netw. 2011 Aug 1;9(8):914-32.

20. Link H, Maschmeyer G, Meyer P, Hiddemann W, Stille W, Helmerking M, Adam D. Interventional antimicrobial therapy in febrile neutropenic patients. Study Group of the Paul Ehrlich Society for Chemotherapy. Ann Hematol. 1994;69:231-43. DOI: 10.1007/BF01700277

21. Schiel X, Link H, Maschmeyer G, Glass B, Cornely OA, Buchheidt D, Wilhelm M, Silling G, Helmerking M, Hiddemann W, Ostermann H, Hentrich M. A Prospective, Randomized Multicenter Trial of the Empirical Addition of Antifungal Therapy for Febrile Neutropenic Cancer Patients: Results of the Paul Ehrlich Society for Chemotherapy (PEG) Multicenter Trial II. Infection. 2006 Jun;34:118-26. DOI: 10.1007/s15010-006-5113-9

22. Elting LS, Rubenstein EB, Rolston KV, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin Infect Dis. 1997 Aug;25(2):247-59. DOI: 10.1086/514550

23. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006 May 15;106:2258-66. DOI: 10.1002/cncr.21847

24. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer. 2005 May 1;103(9):1916-24. DOI: 10.1002/cncr.20983

25. Diehl V, Franklin J, Pfreundschuh M, Lathan B, Paulus U, Hasenclever D, Tesch H, Herrmann R, Dörken B, Müller-Hermelink HK, Dühmke E, Loeffler M; German Hodgkin's Lymphoma Study Group. Standard and Increased-Dose BEACOPP Chemotherapy Compared with COPP-ABVD for Advanced Hodgkin's Disease. N Engl J Med. 2003 Jun 12;348:2386. DOI: 10.1056/NEJMoa022473

26. Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, Rübe C, Rudolph C, Reiser M, Hossfeld DK, Eimermacher H, Hasenclever D, Schmitz N, Loeffler M; German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood. 2004 Aug 1;104(3):634-41. DOI: 10.1182/blood-2003-06-2095

27. Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, Rudolph C, Reiser M, Hossfeld DK, Metzner B, Hasenclever D, Schmitz N, Glass B, Rübe C, Loeffler M; German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood. 2004 Aug 1;104(3):626-33. DOI: 10.1182/blood-2003-06-2094

28. Schmitz N, Kloess M, Reiser M, Berdel WE, Metzner B, Dorken B, Kneba M, Trumper L, Loeffler M, Pfreundschuh M, Glass B; German High-Grade Non Hodgkin's Lymphoma Study Group (DSHNHL). Four versus six courses of a dose-escalated cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen plus etoposide (megaCHOEP) and autologous stem cell transplantation: early dose intensity is crucial in treating younger patients with poor prognosis aggressive lymphoma. Cancer. 2006 Jan 1;106(1):136-45. DOI: 10.1002/cncr.21588

29. Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C, Kuhn W, Nitz U, Schneeweiss A, Huober J, Harbeck N, von Minckwitz G, Runnebaum IB, Hinke A, Kreienberg R, Konecny GE, Untch M. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol. 2010 Jun 10;28(17):2874-80. DOI: 10.1200/JCO.2009.24.7643

30. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, Moore A, Ellerton JA, Norton L, Ferree CR, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med. 1994 May 5;330(18):1253-9. DOI: 10.1056/NEJM199405053301801

31. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med. 1995 Apr 6;332(14):901-6. DOI: 10.1056/NEJM199504063321401

32. Budman DR, Berry DA, Cirrincione CT, Henderson IC, Wood WC, Weiss RB, Ferree CR, Muss HB, Green MR, Norton L, Frei E 3rd. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst. 1998 Aug 19;90(16):1205-11. DOI: 10.1093/jnci/90.16.1205

33. Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C, Kuhn W, Nitz U, Schneeweiss A, Huober J, Harbeck N, von Minckwitz G, Runnebaum IB, Hinke A, Kreienberg R, Konecny GE, Untch M. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol. 2010 Jun 10;28(17):2874-80. DOI: 10.1200/JCO.2009.24.7643

34. Kwak LW, Halpern J, Olshen RA, Horning SJ. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. J Clin Oncol. 1990 Jun;8(6):963-77.

35. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol. 2010 May 1;28(13):2191-7.

36. Crawford J, Althaus B, Armitage J, Blayney DW, Cataland S, Dale DC, Demetri GD, Foran J, Heaney ML, Htoy S, Kloth DD, Lyman GH, Michaud L, Motl S, Vadhan-Raj S, Wong MK; National Comprehensive Cancer Network. Myeloid growth factors clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2005 Jul;3:540-55.

37. Chouaid C, Bassinet L, Fuhrman C, Monnet I, Housset B. Routine use of granulocyte colony-stimulating factor is not cost-effective and does not increase patient comfort in the treatment of small-cell lung cancer: an analysis using a Markov model. J Clin Oncol. 1998 Aug;16(8):2700-7.

38. Crawford J, Wolff DA, Culakova E, Poniewierski MS, Selby C, Dale DC, Lyman GH; ANC Study Group. First Cycle Risk of Severe and Febrile Neutropenia in Cancer Patients Receiving Systemic Chemotherapy: Results from a Prospective Nationwide Study. Blood (ASH Annual Meeting Abstracts). Nov 2004;104:2210.

39. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, Lyman GH, Pettengell R, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C; European Organisation for Research and Treatment of Cancer. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011 Jan;47(1):8-32. DOI: 10.1016/j.ejca.2010.10.013

40. Shayne M, Culakova E, Poniewierski MS, Wolff D, Dale DC, Crawford J, Lyman GH. Dose intensity and hematologic toxicity in older cancer patients receiving systemic chemotherapy. Cancer. 2007 Aug 17;110:1611-20. DOI: 10.1002/cncr.22939

41. Pettengell R, Gurney H, Radford JA, Deakin DP, James R, Wilkinson PM, Kane K, Bentley J, Crowther D. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. Blood. 1992;80:1430-6.

42. Trillet-Lenoir V, Green J, Manegold C, Von Pawel J, Gatzemeier U, Lebeau B, Depierre A, Johnson P, Decoster G, Tomita D, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer. 1993;29A:319-24. DOI: 10.1016/0959-8049(93)90376-Q

43. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. Am J Med. 2002 Apr 1;112(5):406-11. DOI: 10.1016/S0002-9343(02)01036-7

44. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of Americaa. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):427-31. DOI: 10.1093/cid/ciq147

45. García-Carbonero R, Mayordomo JI, Tornamira MV, López-Brea M, Rueda A, Guillem V, Arcediano A, Yubero A, Ribera F, Gómez C, Trés A, Pérez-Gracia JL, Lumbreras C, Hornedo J, Cortés-Funes H, Paz-Ares L. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. J Natl Cancer Inst. 2001 Jan 3;93(1):31-8. DOI: 10.1093/jnci/93.1.31

46. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol. 2005 Jun 20;23(18):4198-214. DOI: 10.1200/JCO.2005.05.645

47. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 2004 Apr 5;116(Suppl 7A):11S-26S. DOI: 10.1016/j.amjmed.2003.12.008

48. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005 Mar 10;352(10):1011-23. DOI: 10.1056/NEJMra041809

49. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med. 1990;322:1689-92. DOI: 10.1056/NEJM199006143222401

50. Wissenschaftlicher Beirat der Bundesärztekammer. Querschnitts-Leitlinien (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten, zuletzt geändert 10.1.2011. 4. Aufl. Berlin: Bundesärztekammer; 2008. S. 1-392. Available from: http://www.baek.de/downloads/Querschnittsleitlinie_Gesamtdokument-deutsch_07032011.pdf [cited 2011 Jan 8]

51. Yazdanbakhsh K, Bao W, Zhong H. Immunoregulatory effects of stored red blood cells. Hematology Am Soc Hematol Educ Program. 2011;2011:466-9. DOI: 10.1182/asheducation-2011.1.466

52. Castillo JJ, Dalia S, Pascual SK. Association between red blood cell transfusions and development of non-Hodgkin lymphoma: a meta-analysis of observational studies. Blood. 2010 Oct 21;116:2897-907. DOI: 10.1182/blood-2010-03-276683

53. Mortensen FV, Jensen LS, Sorensen HT, Pedersen L. Cause-specific mortality associated with leukoreduced, buffy coat-depleted, or no blood transfusion after elective surgery for colorectal cancer: a posttrial 15-year follow-up study. Transfusion. 2011 Feb;51:259-63. DOI: 10.1111/j.1537-2995.2010.02825.x

54. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood. 2009 Apr 9;113:3406-17. DOI: 10.1182/blood-2008-10-167643

55. Vamvakas EC, Blajchman MA. Blood Still Kills: Six Strategies to Further Reduce Allogeneic Blood Transfusion-Related Mortality. Transfusion Medicine Reviews. 2010 Apr;24:77-124. DOI: 10.1016/j.tmrv.2009.11.001

56. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, Bennett CL, Bohlius J, Evanchuk D, Goode MJ, Jakubowski AA, Regan DH, Somerfield MR; American Society of Clinical Oncology; American Society of Hematology. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol. 2010 Nov 20;28(33):4996-5010. DOI: 10.1200/JCO.2010.29.2201

57. Aapro M, Link H. Update on EORTC guidelines and anemia management with erythropoiesis stimulating agents (ESAs). Oncologist. 2008;13(Suppl 3):33-6. DOI: 10.1634/theoncologist.13-S3-33

58. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, Chesney M, Clark-Snow RA, Flaherty AM, Freundlich B, Morrow G, Rao KV, Schwartz RN, Lyman GH; American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2011 Nov 1;29:4189-98. DOI: 10.1200/JCO.2010.34.4614

59. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Rittenberg C, Saito M, Tonato M, Warr D; ESMO/MASCC Guidelines Working Group. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010 May 1;21:v232-43. DOI: 10.1093/annonc/mdq194

Corresponding author:
Prof. Dr. med. Hartmut Link
Klinik für Innere Medizin I, Westpfalz-Klinikum,
Hellmut-Hartert-Str. 1, 67655 Kaiserslautern, Germany
hlink@rhrk.uni-kl.de

Please cite as
Link H. Supportive therapy in medical therapy of head and neck tumors. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2012;11:Doc01.
DOI: 10.3205/cto000083, URN: urn:nbn:de:0183-cto0000834

This article is freely available from
http://www.egms.de/en/journals/cto/2012-11/cto000083.shtml

Published: *2012-12-20*