CLINICAL PRACTICE GUIDELINE

Supportive Treatments for Patients with Cancer

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SUMMARY

Background: For the treatment of patients with cancer to be successful and well-tolerated, the complications and side effects of the disease and its treatment must be treated and limited as far as possible. Summarized recommendations based on the constantly increasing evidence in the area of supportive care must be defined, standardized, and communicated.

Methods: We systematically reviewed the literature on the topics of anemia, neutropenia, nausea/vomiting, diarrhea, oral mucositis, skin toxicity, and peripheral neurotoxicity induced by cancer treatment, as well as osseous complications, extravasation, and side effects of radiotherapy. Recommendations were approved in a moderated, formalized consensus procedure.

Results: In patients suffering from chemotherapy-induced anemia, the administration of agents that stimulate erythropoiesis can be considered. This can potentially improve these patients' quality of life and lessen the frequency of blood transfusions, but it can also lead to thromboembolic complications and arterial hypertension. If only a single individual risk factor is present in a patient whose risk of febrile neutropenia is estimated at 10–20%, there is no obligatory indication for the administration of granulocyte-colony stimulating factor. Antiemetic treatment before carboplatin is given can consist of a neurokinin-1 receptor antagonist along with a setron and dexamethasone. Duloxetine is recommended for the treatment of neuropathic pain. Sensorimotor training is effective in the treatment of chemotherapy-induced peripheral neuropathy and can already be given at the same time as the chemotherapy. Women with bony metastases of breast cancer who have been taking zoledronate at four-week intervals for a year should take it at 12-week intervals from then onward in order to lessen the likelihood of osseous complications. There is no evidence for any effective prophylactic treatment of chemotherapy-induced diarrhea.

Conclusion: Supportive measures are an integral component of all oncological treatments. More research is needed to determine how side effects can be lessened and prevented.

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Every year around half a million residents of Germany are diagnosed with cancer (1). For many of them, the treatment of their malignant disease is associated with serious side effects that severely impair their quality of life. Effective supportive measures enable successful specific management of the cancer by dealing with any complications of the disease and its treatment. This guideline discusses the evidence for the supportive care of 10 major complications of tumor therapy in order to standardize and optimize inter- and multidisciplinary care.

Method

The S3 guideline on supportive care for patients with cancer was drawn up under the aegis of the German Cancer Society (Working Group for Supportive Care in Cancer, Rehabilitation, and Social Medicine within the German Cancer Society [*Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin*/ASORS]), the German Society for Hematology and Medical Oncology (*Deutsche Gesellschaft für Hämatologie und medizinische Onkologie*/DGHO), and the German Society for Radiooncology (*Deutsche Gesellschaft für Radioonkologie*/DEGRO). The work on the guideline was funded by the German Guideline Program Oncology of German Cancer Aid (*Deutsche Krebshilfe*/DKH).

The guideline aims to be of assistance to the members of all disciplines and professions involved in the treatment of patients with cancer, as well as to the patients themselves. More than 90 elected representatives and experts participated in its compilation (*eTable 1*).

A total of 120 key questions were agreed and formulated (see PRISMA diagram [PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses] in *eFigure 1*). The resulting recommendations and accompanying explanatory texts were agreed at two consensus conferences.

Results

Current, evidence-based international guidelines on the following topics were updated and modified:

- Tumor Therapy-induced Nausea and Vomiting (Multinational Association of Supportive Care in Cancer/MASCC) (2)
- Oral Mucositis (MASCC) (3)

TABLE 1

Recommendation and consensus strengths in the S3 guideline

Recommendation strength	Description	Expressed as
A	Strong recommendation	Should
B	Recommendation	Ought to
O	Recommendation open	May
Consensus strength	Percentage agreement	
Strong consensus	>95 % of those entitled to vote	
Consensus	>75–95 %	
Majority agreement	50–75 %	
Disagreement	<50 %	

- Prophylaxis of Tumor Therapy-induced Febrile Neutropenia with Granulopoietic Growth Factors (DGHO [4], American Society of Clinical Oncology/ASCO [5])
- Therapy-Induced Osteoporosis (Osteology Federation (*Dachverband Osteologie/DVO*) (6).

The topic of supportive measures in radiooncology (a section of the S2e guideline on radiooncology) (7) was updated and its content expanded. The quality and quantity of studies differed greatly. While there were numerous randomized controlled trials (RCTs) for anemia/erythropoiesis-stimulating agents (ESA), with a large number of patients overall ($n > 13\,000$), for the section on extravasation we had to resort to case series. The evidence was assessed according to the Oxford scheme of 2009. For two particularly controversial issues (anemia/ESA, bisphosphonates/receptor activator of nuclear factor- κ B (RANK) ligand antibodies in osseous complications), the evidence was assessed according to Grading Recommendations Assessment, Development and Evaluation (GRADE) by the Cochrane Haematological Malignancies Group, Cologne. In the following, the recommendation strength and evidence quality (*Table 1*), or EC for expert consensus, are given in parentheses.

Anemia induced by cancer treatment

The anemia often found in cancer patients can arise from the disease or from the treatment (8). Depending on the type and stage of the tumor, anemia is already present at the time of diagnosis in 31 to 50% of patients with solid tumors. The prevalence in hematological neoplasms is even higher (9). The appropriate treatment depends on the clinical constellation and may comprise blood transfusion, ESA, or, in the case of functional iron deficiency, intravenous substitution.

Erythropoiesis-stimulating agents

Assessment of the evidence was based on a Cochrane Review from 2012 (10) and subsequent research (11–14). In line with the current licensing of ESA, we

excluded studies of anemia caused by radiotherapy or radiochemotherapy and those in which ESA was given at a hemoglobin (Hb) value > 10 g/dL (6.2 mmol/L) and then evaluated the data according to GRADE. In accordance with GRADE, the quality of the evidence was classified into four categories, from ++++ for high quality to +--- for very low quality (*eTable 2*). Quality of life, nominated by the elected representatives as the most important endpoint, was recorded in only one study but showed a clinically and statistically significant effect of ESA ($n = 290$; mean difference 6.60; 95% confidence interval [3.92; 9.28]; $p < 0.0001$; +---). No differences among groups were found for either mortality in the study period or overall survival (OS). Thromboembolism (14 studies, relative risk [RR] 1.53 [1.02; 2.31]; $p = 0.04$; 12 thromboembolic events more per 1000 patients treated with ESA than in the control arm) and high blood pressure (14 studies, $n = 2564$; RR 2.05 [1.32; 3.18]; $p = 0.001$) occurred more frequently. In summary, ESA can be considered for the treatment of chemotherapy-induced anemia (O, +---). The potential benefits (improved quality of life, reduced transfusion frequency) and risks (thromboembolic complications, high blood pressure) should definitely be discussed with the patient (A, +---).

Transfusion

In line with the German Medical Association's (*Bundesärztekammer, BÄK*) horizontal guideline on treatment with blood components (15), patients with cancer treatment-induced anemia can be considered for transfusion if their hematocrit (HC) is below 21 to 24% or they have an Hb concentration < 7 –8 g/dL (< 4.3 –5.0 mmol/L) (EC). In hospitalized patients whose HC or Hb is only slightly below the trigger level, only packed red cells should be transfused.

Neutropenia induced by cancer treatment

The importance of individual risk factors that might justify the use of granulocyte colony-stimulating factors (G-CSF) in the presence of a 10 to 20% risk of febrile neutropenia was systematically assessed. A consensus was reached that no specific risk factor can be clearly identified and that probably a combination of several risk factors is required to increase the likelihood of febrile neutropenia (*Table 2*). The simple presence of afebrile neutropenia following treatment for cancer does not justify administration of G-CSF (EC).

Nausea and vomiting induced by cancer treatment

As a prophylactic measure, patients being treated with highly emetogenic chemotherapy (risk of vomiting $> 90\%$) should definitely be given a 5-hydroxytryptamine (5-HT) $_3$ receptor antagonist, a neurokinin (NK) $_1$ receptor antagonist, and dexamethasone (A, 1a) (*Table 3*). In the case of moderately emetogenic chemotherapy (risk of vomiting 30 to 90%), prophylaxis with 5-HT $_3$ receptor antagonists and dexamethasone is indicated

(A, 1a). Carboplatin is a special case: in addition to 5-HT₃ receptor antagonists and dexamethasone (A, 1a), an NK1 receptor antagonist can be given (0, 1a). Prophylaxis with a 5-HT₃ receptor antagonist, an NK1 receptor antagonist, and dexamethasone should also ensue in chemotherapy extending over several days (cisplatin, etoposide, bleomycin [PEB]) or in high-dose chemotherapy with melphalan. In the event of inadequately controlled nausea and vomiting, olanzapine should be preferred to metoclopramide as rescue antiemetic (off-label use) (B, 1a) (*eTable 3*). In a study of 108 patients randomized to receive olanzapine or metoclopramide after failure of antiemetic prophylaxis, no further vomiting occurred in 70% and 31% of cases respectively (16).

Diarrhea induced by cancer treatment

For no form of medicinal cancer treatment could effective prevention of diarrhea be demonstrated. The following agents should definitely not be given: budesonide (A, 2b), healing earth (A, 1b), ciclosporin A (A, 1b), glutamine (A, 2b), neomycin (A, 1b), and octreotide (A, 1b). In one study on prevention of 5-fluorouracil-induced diarrhea, the patients (n = 150) received synbiotics or placebo. Those in the intervention group (n = 97) were less likely than those in the placebo group (n = 51) to suffer diarrhea grade 3/4 (21/97 versus 19/51, odds ratio [OR] 0.47 [0.22; 0.98]) (17). The weakest form of recommendation was agreed for prophylaxis with synbiotics/probiotics (0, 1b). Highly immunosuppressed patients are an exception to this recommendation.

Uncomplicated diarrhea (grades 1 and 2 without risk factors) should be treated symptomatically with loperamide (EC), intensified if necessary with octreotide (off-label use) (EC, see algorithm in *eFigure 2*).

In refractory cases of diarrhea, one should consider escalating electrolyte and fluid adjustment by adding tincture of opium*, budesonide*, racecadotril, or oral aminoglycosides* (*off-label use) (EC).

Mucositis induced by cancer treatment

The only drugs that can be recommended for the prevention of radiogenic oral mucositis are benzydamine (B, 2b) and zinc (0, 2b). All other substances, e.g., sucralfate (A, 1a) and intravenously (i.v.) administered glutamine (A, 1c), have recommendations against their use. Basic oral care remains the most important measure, with regular mouthwashes and clinical examinations accompanied by preventive professional dental cleaning (A, 2b). Cryotherapy (sucking ice cubes) can be recommended for chemotherapy with bolus administration of 5-fluorouracil (A, 1c) and for high-dose melphalan in patients on high-dose treatment for stem cell transplantation (0, 1b). Intra-oral low-level laser treatment can be considered for prophylaxis of radiogenic oral mucositis (0, 1b).

In the treatment of oral mucositis the recommendations relate to control of symptoms. This takes the form of systemic opioid-based medication (A, 1c); al-

TABLE 2

Summary of the risk of febrile neutropenia, the prophylactic administration of granulocyte colony-stimulating factor, and the individual risk factors

Risk of febrile neutropenia	Recommendation* (of varying strength)
> 40 %	G-CSF
> 20–40 %	G-CSF
10–20 % with individual RF	G-CSF
10–20 % without individual RF	No G-CSF
<10 %	No G-CSF

Consensus-based statement on individual risk factors

No individual risk factor can be clearly specified. The following factors, particularly in combination, probably elevate the risk of febrile neutropenia:

- Age >65 years
- Low performance status (low Karnofsky index, high ECOG scale score)
- Comorbidities (COPD, heart failure NYHA III–IV, HIV infection, autoimmune disease, severely impaired renal function)
- Advanced symptomatic tumor disease
- Previous chemotherapy
- Laboratory test results (anemia, lymphocytopenia <700/μL, hypalbuminemia, hyperbilirubinemia)

The assessment also took account of other study endpoints, e.g., infection-related mortality.

COPD, Chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus; NYHA, New York Heart Association; RF, risk factors

* These recommendations are not valid for patients with leukemia and myelodysplastic syndrome.

ternatively, for radiogenic mucositis, a morphine mouthwash can be used (0, 2b).

Skin toxicity induced by cancer treatment

Acneiform exanthema/rash

The prevention of acneiform exanthema during treatment with epidermal growth factor receptor (EGFR) inhibitors is achieved by behavioral adaptation and basic care measures, such as avoidance of mechanical and chemical noxae, adequate protection from ultraviolet rays, and application of skin cream containing 5 to 10% urea (A, 5). Moreover, oral tetracycline (minocycline or doxycycline) should be given prophylactically to reduce the severity of the acneiform exanthema (1, 2b).

Acneiform exanthema is treated according to the severity based on Common Terminology Criteria for Adverse Events (CTCAE) (*Table 4*). It is important to interrupt treatment of acneiform exanthema of grade 3 or 4 (EC).

Hand-foot syndrome

Prevention of palmar–plantar erythrodysesthesia, or hand–foot syndrome (HFS), is also primarily achieved by avoidance of mechanical overload and use of urea skin cream (B, 1b). During infusion of docetaxel, cooling of the hands and feet can help to minimize HFS (0, 2b). Nail toxicity can also be avoided by this means (B, 2b). In the study by Scotte et al. (18), patients cooled one hand for 90 min during docetaxel treatment. The rate of occurrence of HFS was lower in the cooled hand

TABLE 3

Summary of acute and delayed antiemetic prophylaxis

Emetogenic risk	Acute phase (before drug treatment of tumor)					Delayed phase (from 24 h after drug treatment of tumor)
High >90%						
Highly emetogenic and AC-based CTX ^{*1}	5-HT3-RA					–
	NK1-RA					*2
	Dexamethasone					Dexamethasone days 2–4
Moderate >30–90%						
Carboplatin-based CTX ^{*4}	5-HT3-RA					–
	NK1-RA ("can")					*2
	Dexamethasone					Optional dexamethasone days 2–3
Moderate (other than carboplatin)	5-HT3-RA					–
	Dexamethasone					*3
Low 10–30%	Dexamethasone	or	5-HT3-RA	or	MCP	–
Minimal <10%	No routine prophylaxis					No routine prophylaxis

*1 Only anthracycline and cyclophosphamide-based chemotherapy in patients with breast cancer is viewed as highly emetogenic.

The CHOP regimen is classified as moderately emetogenic.

*2 Administration of aprepitant on days 2 and 3 according to conditions of approval; administration of fosaprepitant or netupitant/palonosetron only on day 1.

*3 Administration of dexamethasone in the delayed phase recommended only in the case of chemotherapy with elevated potential for delayed vomiting, e.g., oxaliplatin, doxorubicin, cyclophosphamide, bendamustine

*4 Randomized studies have been published only for combination treatments with carboplatin AUC >4.

AC, Anthracycline cyclophosphamide; AUC, area under the curve; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CTX, chemotherapy; HT, hydroxytryptamine; NK, neurokinin; MCP, metoclopramide; RA, receptor antagonist

(24%) than in the uncooled hand (53%) ($p = 0.0001$). Neither topical Mapiisal (an ointment containing several antioxidants and exhibiting high radical protection factor, available in Germany since 2011) (A, 1b; during treatment with capecitabine) nor pyridoxine (A, 1a) had a prophylactic effect.

In HFS of grade 3 or worse, the dose of the substance responsible should definitely be reduced or the interval between treatments increased (A, 5). Anti-inflammatory treatment with topical glucocorticoids (class 2–3) should be applied (B, 5), and local hydrocolloid bandages can be used (0, 2b) (Table 4). The guideline includes recommendations for pruritus, alopecia, and nail changes.

Peripheral neurotoxicity induced by cancer treatment

There exists no effective drug treatment to prevent chemotherapy-induced polyneuropathy (CIPN). This includes the prophylactic administration of acetylcysteine (A, 1b), α -lipoic acid (A, 1b), amifostine (B, 1a), calcium and magnesium (B, 1a), carbamazepine (B, 1b), glutathione (A, 1a), and vitamin E (B, 1a). Training to improve coordination, sensorimotor, and fine motor function should begin (at the latest) with the onset of manifest CIPN, but can be started earlier, at the time when potentially neurotoxic cancer treatment is initiated (EC). Smith et al. gave 231 patients with painful CIPN either duloxetine or placebo (19) and found a higher rate of pain reduction for duloxetine (59% versus 38%). Duloxetine is thus recommended for the treatment of

neuropathic pain (B, 1b) (off-label use). In analogy to polyneuropathy from other causes, the use of amitriptyline (0, 1b), gabapentin (0, 1b), pregabalin (EC), or venlafaxine (EC) can be considered.

Osseous complications

Osseous manifestations of the malignant disease

The site and symptoms of osseous manifestations and their potential complications determine the form taken by interdisciplinary cooperation in the overall oncological concept. In the presence of stable osseous manifestations with no sign of spinal cord compression, conservative treatment is indicated (EC), e.g., systemic tumor treatment, radiotherapy, radionuclide therapy, or bisphosphonates/RANK ligand antibodies. If pressure is being exerted on the spinal cord, surgery followed by radiotherapy or radiotherapy alone can be discussed (B, 1b). The decision on what treatment to initiate depends on the type of underlying disease, the operability of the tumor, and the likelihood of neurological remission. If the situation is unstable, initial surgical stabilization should be performed, followed in most cases by radiotherapy, provided these interventions can be carried out and a positive effect in terms of quality of life and/or survival can be anticipated (EC).

In the case of painful bony metastases the first medicinal intervention is adequate analgesia. Furthermore, osteoprotective treatment can delay or prevent skeletal related events (SRE) (0, 1a). In both breast cancer and prostate cancer with osseous

metastases, administration of denosumab leads to a numerically small but statistically significant reduction in SRE compared with zoledronate. For other outcome parameters, such as pain, spinal cord compression, mortality, and osteonecrosis of the jaw, there is no evidence of any difference between the two drugs. For other solid tumors, the data comparing denosumab with bisphosphonates are too sparse with regard to SRE (*eTable 4*) (20–23). Studies on the dose intervals for bisphosphonates (24–26) showed that after monthly bisphosphonate treatment for at least 1 year, the rates of SRE were almost identical for continued 4-weekly (22%) and 12-weekly (23.2%) administration of zoledronate. In patients with osseous metastases of breast cancer, therefore, 1 year of zoledronate treatment at 4-weekly intervals should definitely be followed by administration of zoledronate every 12 weeks (A, 1a; evidence quality for other tumors B, 1b).

Treatment-associated osteoporosis

Initiation of antihormonal treatment, therapy-induced premature menopause or long-term steroid treatment in cancer patients are grounds for a basic diagnostic work-up (*eTable 5*) to ensure timely determination of the indication for treatment of osteoporosis. Recently published data (27, 28) indicate a higher risk of osteoporosis than previously assumed in patients receiving estrogen- and androgen-suppressing treatment. Therefore, from now on antiresorptive treatment should definitely be initiated whenever bone marrow density is <-1.5 (EC).

Extravasation

Extravasation of drugs for tumor treatment is a serious but largely avoidable iatrogenic event.

Choice of a suitable vessel for infusion (not near a joint, no multiple punctures in the same area), together with verification of position by aspiration and rinsing, safe but visible fixation of the vascular access, and ensuring the patient knows how to recognize the symptoms of extravasation, goes a long way to preventing this complication.

Antidotes are available for a small number of substances. Mouridsen et al. investigated the administration of dexrazoxane i.v. in 80 patients with extravasation of anthracycline and reported that surgical intervention could be avoided in 98.2% of cases (29). Extravasation of anthracycline should be followed by administration of dexrazoxane (B, 2a). In the event of extravasation of amsacrine, cisplatin, dactinomycin, or mitomycin C, the extravasation site is dabbed with 99% dimethylsulfoxide (B, 3a). Extravasation of vinca alkaloids should be treated by subcutaneous perilesional injection of hyaluronidase (B, 3b). Every cancer treatment unit should possess an extravasation emergency kit containing precise instructions on how to proceed in the case of extravasation together with the necessary materials and antidote drugs (EC).

TABLE 4

Common Terminology Criteria for Adverse Events: treatment of cutaneous toxicity according to severity

Treatment of acneiform exanthema	Treatment of pruritus	Treatment of hand-foot syndrome (HFS)
<p>Acneiform exanthema CTCAE grade 1 (B, 5):</p> <ul style="list-style-type: none"> – Basic measures including oral antibiotics and – Topical application of antibiotic-containing cream 2 × daily (e.g., metronidazole, nadifloxacin) 	<p>Pruritus CTCAE grade 1 (B, 5):</p> <ul style="list-style-type: none"> – Continuation of basic measures – External lipid-replenishing agents and – Consider oral antihistamines 	<p>HFS CTCAE grade 1–2:</p> <ul style="list-style-type: none"> – Avoidance of mechanical overloading and chemical noxae (A, 5) – Treatment of pre-existing diseases such as intertrigo, necrosis, mycosis, hyperkeratosis (A, 5) – Urea-containing cream 5–10% at least 2 × daily (B, 1b) – Cooling of hands and feet during docetaxel infusion (0, 2b)
<p>Acneiform exanthema CTCAE grade 2 (B, 5):</p> <ul style="list-style-type: none"> – As for grade 1 plus – Topical application of glucocorticoids class 2–3 (e.g., prednicarbate cream) 	<p>Pruritus CTCAE grade 2 (B, 5):</p> <ul style="list-style-type: none"> – External lipid-replenishing agents and – Oral antihistamines and – Consider topical glucocorticoid class 2 (e.g., prednicarbate cream) 	
<p>Acneiform exanthema CTCAE grade 3/4 (B, 5):</p> <ul style="list-style-type: none"> – Treatment together with a dermatologist – Dose modification or treatment interruption according to manufacturer's advice – As for grade 2 and further treatment options: <ul style="list-style-type: none"> – systemic glucocorticoids – systemic antibiotic treatment according to antibiogram – if indicated, oral isotretinoin* 	<p>Pruritus CTCAE grade 3 (B, 5):</p> <ul style="list-style-type: none"> – External lipid-replenishing agents and – Oral antihistamines and – Topical glucocorticoid class 2 (e.g., prednicarbate cream) 	<p>HFS CTCAE grade 3/4 (A, 5):</p> <ul style="list-style-type: none"> – Substance-dependent widening of the interval between treatments/ dose reduction (A, 5) – Anti-inflammatory treatment with topical glucocorticoids class 2–3 (B, 5) – Plantar hydrocolloid bandage (0, 2b)

CTCAE, Common Terminology Criteria for Adverse Events

*Isotretinoin is not to be combined with systemic antibiotic treatment owing to the danger of life-threatening cerebral edema

Supportive measures in radiooncology

Irradiation of the upper abdomen, the pelvis, or the rectum can lead to diarrhea as a result of enteropathy, enteritis, or proctitis.

There are limited data showing a positive effect of sulfasalazine in the prophylaxis of radiogenic diarrhea (0, 1b). Administration of amifostine before every fraction can decrease the incidence and intensity of diarrhea from acute radiogenic enteritis (0, 2b), and an amifostine enema can reduce the risk of acute radiogenic proctitis (0, 2b). Rectal administration of mesalazine, olsalazine, and misoprostol should be avoided owing to the assumed increased risk of complications (A, 1b).

In analogy to diarrhea after chemotherapy, loperamide is advised for treatment of radiogenic diarrhea (B, 2b); if loperamide has no effect, tincture of opium is recommended (B, 5).

Radiogenic xerostomia blunts the sense of taste and hampers speech and swallowing, thus potentially

leading to malnutrition and dental disease. The decisive factor in prophylaxis of xerostomia is the radiation dose for the salivary glands, which should definitely be minimized by using appropriate irradiation techniques, e.g., intensity-modulated radiotherapy (IMRT) (A, 2b). One drug that can be used to prevent radiogenic xerostomia is amifostine (O, 1b). Pilocarpine is available for treatment of xerostomia (A, 1b). Furthermore, there are various artificial saliva products, all with similar efficacy (O, 2b).

For prevention of radiotherapy-induced nausea and vomiting, highly emetogenic radiotherapy (whole-body irradiation) should definitely be accompanied by administration of 5-HT₃ receptor antagonists and dexamethasone (A, 2a), moderately emetogenic radiotherapy (upper abdomen, thoracic/lumbar spine) by a 5-HT₃ receptor antagonist (B, 1b). The additional administration of dexamethasone can be considered (O, 1b).

The topics of radiodermatitis, osteoradionecrosis, radiogenic pneumonitis, and sequelae of irradiation of the brain and spinal cord were taken from the previously S2e guideline on supportive care in radiooncology (7), updated, and agreed; they are not discussed further here.

Conclusion

The number and quality of studies investigating supportive care for patients with cancer vary widely. For some areas (anemia, osseous complications), the strength of recommendation is qualified by the large number of RCTs in the meta-analysis. In other areas (polyneuropathy, diarrhea, mucositis), studies demonstrate a prophylactic effect for only a small number of the numerous substances tested. The full guideline text, methods report, and evidence tables can be found (in German) at leitlinienprogramm-onkologie.de/supportive-therapie.95.0.html.

KEY MESSAGES

- In tumor therapy-induced anemia, transfusion can be considered if the hematocrit level sinks to under 21 to 24% or the hemoglobin concentration goes down to less than 7–8 g/dL (4.3–5.0 mmol/L).
- Afebrile neutropenia with no further risk factors does not justify administration of granulocyte colony-stimulating factor.
- The following agents should not be given for prevention of tumor therapy-induced diarrhea: budesonide, healing earth, ciclosporin A, glutamine, neomycin, octreotide.
- The treatment of acneiform exanthema depends on the severity; in grade 3 or worse, the treatment should definitely be interrupted.
- To avoid extravasation, infusions should not be given near a joint and multiple punctures should not be made in the same area. Control of position by aspiration and rinsing is essential.

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Supplementary material:

eTables, eFigures:

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Supplementary material to:

Supportive Treatments for Patients with Cancer

by Karin Jordan, Petra Feyer, Ulrike Höller, Hartmut Link, Bernhard Wörmann, and Franziska Jahn

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eTABLE 1

Medical societies, organizations and experts represented in the guideline group

Societies and organizations	Selected representative(s)
Societies	
German Society of Hematology and Medical Oncology (DGHO)	Prof. Oliver Cornely Prof. Karin Jordan PD Dr. Ulrich Schuler PD Dr. Jörg-Janne Vehreschild Prof. Bernhard Wörmann
German Society of Radiation Oncology (DEGRO)	PD Dr. Ulrike Höller Dr. Maria Steingraber
German Dermatological Society (DDG)	PD Dr. Carmen Loquai
German College of General Practitioners and Family Physicians (DEGAM)	Dr. Peter Engeser
German Surgical Society (DGCH)	PD Dr. Ulrich Ronellenfitsch
German Society of Obstetrics and Gynecology (DGGG)	Prof. Jens Huober (represented at first CC by Dr. Eva Stauss)
German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNOKHC)	PD Dr. Georgios Psychogios (Prof. Johannes Zenk)
German Society of Internal Medicine (DGIM)	PD Dr. Karin Hohloch (represented at second CC by Dr. Tobias Overbeck)
German Society for Oral and Maxillofacial Surgery (DGMKG)	Prof. Bilal Al-Nawas Prof. Knut Grötz (represented at first and second CC by Dr. Maximilian Krüger)
German Society of Neurosurgery (DGNC)	PD Dr. Dorothee Wiewrodt
German Neurological Society (DGN)	Prof. Roman Rolke (Prof. Raymond Voltz)
German Society of Nuclear Medicine (DGN)	Prof. Holger Palmedo
German Society for Oncological Pharmacy (DGOP)	Michael Höckel
German Association for Orthopaedics and Orthopaedic Surgery (DGOOC)	Prof. Jendrik Harges
German Society of Osteology (DGO)	Prof. Franz Jakob
German Society for Palliative Medicine (DGP)	PD Dr. Bernd Alt-Epping (represented at second CC by Prof. Birgit van Oorschot)
German Respiratory Society (DGP)	Prof. Christian Grohé
German Society of Rehabilitation Science (DGRW)	Prof. Holger Schulz
German Society for Transfusion Medicine and Immunohematology (DGTI)	Prof. Hubert Schrezenmeier (represented at second CC by Prof. Birgit Gathof)
German Society of Urology (DGU)	PD Dr. Chris Protzel
German Society of Digestive and Metabolic Diseases (DGVS)	Prof. Patrick Michl
German Cancer Society (DKG)	Prof. Petra Feyer Dr. Christa Kerschgens Prof. Karin Jordan Prof. Hartmut Link
German Society for Osteoncolology (DOG)	Prof. Ingo J. Diel
German Society of Radiology (DRG)	Prof. Marc-André Weber (represented at second CC by Dr. Simon D. Sprengel)
German Pain Society	PD Dr. Stefan Wirz (represented at first CC by Dr. Michael Schenk)

Societies and organizations	Selected representative(s)
Society for Paediatric Oncology and Haematology (GPOH)	Prof. Thomas Lehnbecher (represented at first and second CC by Dr. Toralf Bernig)
Austrian Society for Haematology and Medical Oncology (OeGHO)	Prof. Ewald Wöll (Dr. Walpurga Weyrer)
Swiss Society of Medical Oncology (SGMO)	Prof. Markus Borer
Working groups and organizations	
German Working Group for Supportive Care in Cancer (ASORS)	Prof. Petra Feyer Dr. Christa Kerschgens Prof. Karin Jordan Prof. Hartmut Link
Dermatological Oncology Working Group (ADO)	Dr. Katharina Kähler
Psycho-Oncology Working Group (PSO)	Dr. Pia Heußner
Working Group for Gynaecological Oncology (AGO)	PD Dr. Joachim Bischoff
Oncology in Internal Medicine Working Group (AIO)	Prof. Maike de Wit Dr. Karin Potthoff
Working Group on Oncological Pharmacy (OPH)	Dr. rer. nat. Annette Freidank
Working Group on Palliative Medicine (APM)	PD Dr. Ulrich Wedding
Working Group on Prevention and Integrative Oncology (PRIO)	Prof. Oliver Micke (represented at second CC by Prof. Birgit van Oorschot)
Working Group on Radiological Oncology (ARO)	Dr. Cornelius Maihöfer
Working Group on Urological Oncology (AUO)	PD Dr. Chris Protzel
Professional Association of Private Practitioners in Hematology and Medical Oncology (BNHO)	Dr. Ingo Schwaner
Professional Association of German Radiation Oncologists (BVDST)	Dr. Dorothea Riesenbeck
Surgical Working Group for Oncology—Abdominal Surgery (CAO-V)	Prof. Daniel Vallböhmer
German Association of Physiotherapists in Germany (ZVK)	Eckhardt Böhle
Haus der Krebs-Selbsthilfe e. V. (HKSH)	Traudl Baumgartner Elke Cario Andrea Hahne Barbara Hübenthal (represented at first CC by Lutz Otto)
Conference of Oncology Nurses and Paediatric Oncology Nurses (KOK)	Dr. Patrick Jahn
Neurooncology Working Group (NOA)	Dr. Susanne Koeppen
Experts	
Dr. Timo Behlendorf; Oliver Blank; Prof. Karl-Stefan Delank; Daniela Dubrau; Grit Gardelegen; Dr. Frank Giordano; Prof. Ralf Gutzmer; PD Dr. Jessica Hassel; Dr. Berit Jordan; Nicola Köhler; Dr. Volker König; Prof. Diana Lüftner; Dr. Regine Mayer-Steinacker; PD Dr. Dipl. Phys. Rotraut Mößner; Prof. Carsten Müller-Tidow; Dr. Sebastian Müller, M. med.; Dr. Petra Örtner; Anja Oschmann; Dr. Sandra Paul; Dr. Michaela Rancea; Dr. Jörn Rüssel; Dr. Lorenz Schlenger; Dr. Oliver Schneider; PD Dr. Nicole Skoetz; Dr. Diana Steinmann; Dr. Friederike Thomasius; Prof. Selma Ugurel; Prof. Dirk Vordermark; Prof. Frederik Wenz; Prof. Frank Zimmermann	
Others	
Dr. Franziska Jahn (guideline office); PD Dr. Susanne Unverzagt (methodology); Jörn Bensch, Dipl.-Ing. (development and maintenance of homepage); Gabriel Appel*; Laura Beck*; Juliane Beckmann*; Moritz Diers*; Jonathan Kühn*; Dr. Camilla Leithold* (project assistant); Katharina Lindner*; Sophie von Wachsmann*; Josephine Werner* (project assistant)	
The following medical societies were offered the opportunity to participate in the guideline process but elected not to send representatives of their own on the grounds that their interests were represented by other societies or working groups: Otorhinolaryngology, Oral and Maxillofacial Surgical Oncology Working Group (AHMO); Germany Society for General and Visceral Surgery (DGAV); German Society of Senology (DGS); German Society of Thoracic Surgery (DGT); German Network for Evidence-Based Medicine (DNEbM); Pneumology-Oncology Working Group (POA)	

CC, Consensus conference

*Assistance with research, data extraction, and data analysis

eTABLE 2

Classification of evidence according to the Oxford criteria or Grading Recommendations Assessment, Development and Evaluation

Classification of evidence according to Grading Recommendations Assessment, Development and Evaluation (GRADE)		
Evidence quality	Description	Symbol
High	Further research is very unlikely to change our confidence in the estimate of effect.	+++
Moderate	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	++
Low	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	+
Very low	Any estimate of effect is very uncertain.	—

eTABLE 3

Reserve antiemetics

Drug	Dose	Licensed for nausea and vomiting
Olanzapine	1 × 5 mg per os (p.o.)	No
Haloperidol	1–3 mg daily	No, but with dose recommendation for vomiting
Metoclopramide	3 × 10 mg p.o. (maximum daily dose 0.5 mg/kg body weight, not exceeding 30 mg in total)	For delayed nausea and vomiting following chemotherapy or radiotherapy
Levomopromazine	3 × 1–5 mg p.o.	No
Alizapride	3 × 50 mg	For vomiting and nausea during treatment with cytostatics
Lorazepam	1 × 1–2 mg p.o.	No
Alprazolam	1 × 0.25–1.0 mg p.o.	No
Dimenhydrinate	3 × 50–100 mg p.o. or 1–2 × 150 mg rectal	For nausea and vomiting of various causes, particularly kinetosis

eTABLE 4

Evidence-based statement on osteoprotective treatment with quality of evidence*¹

Evidence-based statement

Denosumab and bisphosphonates are available for osteoprotective treatment*².

In patients with osseous metastases of breast cancer or prostate cancer, administration of denosumab versus zoledronate leads to a reduction in SRE that is low in absolute terms but statistically significant.

For other outcome parameters, e.g., pain, QoL, spinal cord compression, mortality, and AE osteonecrosis of the jaw, there is no evidence of a difference.

There are no data comparing denosumab with other bisphosphonates.

The data comparing denosumab with bisphosphonates for other solid tumors are inadequate with regard to the endpoint SRE.

Denosumab is not licensed for patients with multiple myeloma; inferiority to zoledronate cannot be excluded.

Endpoint	Breast cancer	Prostate cancer	Other solid tumors and multiple myeloma
SRE	GRADE: +++	GRADE: +++	GRADE: +++
Pain	GRADE: no meta-analysis possible	GRADE: no meta-analysis possible	GRADE: no meta-analysis possible
QoL	GRADE: no meta-analysis possible	GRADE: no meta-analysis possible	GRADE: no meta-analysis possible
Spinal cord compression	GRADE: ++	GRADE: ++	Outcome not reported in study
Mortality	GRADE: +++	GRADE: +++	GRADE: +++
AE osteonecrosis	GRADE: ++	GRADE: ++	GRADE: ++
Outcome of plenary discussion	Consensus (breast cancer, prostate cancer); strong consensus (other solid tumors, multiple myeloma)		

AE, Adverse events; GRADE, Grading Recommendations Assessment, Development and Evaluation; QoL, quality of life; SRE, skeletal related events

*¹ According to GRADE

*² Denosumab licensed only for patients with solid tumors (as of December 2016)

eTABLE 5

Recommendations on the indications for a basic diagnostic work-up for osteoporosis in patients receiving treatment for cancer and the investigations that should be performed

A basic diagnostic work-up for osteoporosis should definitely be performed in patients receiving treatment for cancer when the following apply:

- Initiation of antihormonal treatment
- Treatment-induced premature menopause
- Long-term steroid treatment
- Further indications will emerge from a prevalent risk profile.

If a basic diagnostic work-up is indicated, the following investigations are recommended:

- Medical history and clinical examination
- DXA bone density measurement
- Basic laboratory tests (serum calcium, serum phosphate, serum sodium, alkaline phosphatase, gammaglutamyltransferase; creatinine clearance, ESR/CRP; blood count, serum protein electrophoresis, TSH, optionally vitamin D₃)
- Consider diagnostic imaging in the presence of clinical signs of osteoporotic vertebral fractures
- Assessment of fall risk in patients aged >70 years; optionally also in younger patients

CRP, C-reactive protein; DXA, dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone

eFIGURE 1

PRISMA diagram for tumor treatment-induced diarrhea

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial

eFIGURE 2

Algorithm for assessment and management of tumor treatment-induced diarrhea (30)

CTCAE, Common Terminology Criteria for Adverse Events

* Risk factors: cramp, nausea/vomiting $\geq$ grade 2 CTCAE, low Karnofsky performance index, high temperature, sepsis, neutropenia, dehydration