Multiple myeloma (plasmocytoma) with FUO and mucositis after autologous stem cell transplantation

Objectives:

1. Course and treatment of multiple myeloma
2. Complications of peripheral blood stem cell transplantation (PBSCT)

▶ Evaluation

The neutropenic phase following a Stem cell transplantation means a high risk for each transplanted patient. This case illustrates the interplay of a calculated antibiotic therapy of a fever of unknown origin (FUO), with measures for mucositis prophylaxis and therapy to prevent the entry of bacteria and their spread in the body during the neutropenic phase. Steeply after escalation of the existing calculated antibiotic therapy, the temperature became lower. The described grade IV mucositis represents both a major risk to the patient and also, a crucial affect on the quality of life. In collaboration with the attending physician mucositis and pain therapy were optimized. The patient was able to leave transplant station cca. four weeks after the transplantation. He has since been in complete remission.

▶ Literature

• Schmoll HJ, Höffken K, Possinger K: Kompendium Internistische Onkologie, 4. Aufl. 2006, Springer Verlag Berlin, Heidelberg

• Berger DP, Engelhardt R, Mertelsmann R: Das Rote Buch, 3. Aufl. 2006, Ecomed Verlagsgesellschaft

• Link H, Bokemeyer C, Feyer P: Supportivtherapie bei malignen Erkrankungen, 2006, Deutscher Ärzte-Verlag

• Keefe D et al.: Updated Clinical Practice Guidelines for the Prevention and Treatment of Mucositis, Cancer (2007) 109(5) S:820-831

• Link H et al.: Antimicrobial therapy of unexplained fever in neutropenic patients, Ann Hematol (2003) 82 (Suppl 2) S:105-117

• Bertz H et al.: Antimicrobial therapy of febrile complications after high-dose chemo-/radiotherapy and autologoushematopoietic stem cell transplantation, Ann Hematol (2003) 82 (Suppl 2) S:167-174

▶ Author

Gerald Hensel,
Universitätsklinikum Leipzig AöR
Submitted: in March 2009

Multiple myeloma (plasmocytoma) with FUO and mucositis after autologous stem cell transplantation

Patient: male, 42 years, height: 180 cm, weight: 67 kg, BSA 1,85 m²

Subjective data/comments	The first signs of his illness in 2006, the patient noticed increasingly stronger back pain of unknown origin. In 2007, he underwent spinal surgery, after which the diagnosis has been made. He experienced momentarily severe pain in the mouth and throat after high-dose chemotherapy with stem cell transplantation. Oral feeding was not possible. He responded with a powerful and prolonged nausea on the administered analgesics. He found pain relief by sucking ice cubes.
Objective data (medical history)	The diagnosis of the disease was made in May 2007 after a spinal operation, found an osteolytic lesion in the lumbar spine. A bone marrow biopsy showed no evidence of a monoclonal plasma cell neoplasia. With only a single collection of degenerated plasma cells in the body it is assumed to be a solitary plasmacytoma. The lumbar vertebrae were locally irradiated with a total dose of 40 Gy. In May 2008 the disease extended. There were found new osteolytic lesions in the lumbar spine, the hip bone, the skull, the eye socket and ribs. The bone marrow was infiltrated by monoclonal plasma cells (multiple myeloma). Furthermore, there was evidence of the typical Bence-Jones proteins in the urine. Diagnosis: IgG kappa multiple myeloma stage IIIA according to Salmon and Durie Hemoglobin ‹8.5 g / dl Calcium› 12 mg / dl Detection of Bence-Jones proteinuria In outpatient sector, the patient received two cycles of chemotherapy, consisting of: Doxorubicin (pegylated liposomal) 30 mg / m² d 4 Bortezomib 1.3 mg / m² d 1, 4, 8, 11 With this therapy the progression of the disease was halted temporarily, while the plasma cell infiltration could not be suppressed (Stable Disease). After extensive consultation the decision for autologous peripheral stem cell transplantation has been made. To obtain his own stem cells they conducted a stem cell mobilization with the following schedule four weeks before the planned transplant date: HD-cyclophosphamide 4000 mg / m² d1 G-CSF 5 mg / kg 300 mg from d7 After hematologic recovery, the patient received two days before the transplant date conditioning with: HD-melphalan 200 mg / m² d -2 * * Day of transplantation = d 0

Multiple myeloma (plasmocytoma) with FUO and mucositis after autologous stem cell transplantation

The patient developed on day 5 after transplantation in the neutropenic phase fever of unknown origin (› 39 ° C) (FUO) with chills and hypotension. According to the in-house guideline the antibiotic prophylaxis was escalating from ciprofloxacin to imipenem / cilastin. The antifungal prophylaxis with fluconazole has been maintained (see dosage prescriptions). Despite the changeover, clinical status has not improved

The patient was enrolled in a randomized, placebo-controlled study, which investigated the use of palifermin for the mucositis prophylaxis after conditioning with HD melphalan. Additional local measures for the prophylaxis of mucositis were allowed by the protocol. Nevertheless, the patient developed a severe, large areas ulcerative mucositis WHO grade IV, which made a total parenteral nutrition necessary. To the scheduled morphine syringe pump, he responded with severe nausea. Even administration of metoclopramide does not lead to significant relief of symptoms.

Prescriptions and treatment goals

Prescriptions	Treatment goals
Imipenem / Cilastin 3 x 500 mg i.v. fluconazole 1 x 400 mg i.v. acyclovir 2 x 500 mg i.v.	Calculated antimicrobial therapy after the onset of FUO
Morphine sulfate 0.8 mg / h i.v.	Relief of pain caused by mucositis
Metoclopramide 10 mg i.v.	Relief medication for nausea
Chlorhexidine mouthwash Betaisodona-mouthwash Ampho-Moronal suspension every 2 hours	Mucositis prophylaxis: Local action in the mouth and throat
esomeprazole 1 x 40 mg i.v.	Mucositis prophylaxis in gastrointestinal
Palifermin / placebo 60µg/kg d -6, -5, -4, 0, 1, 2	Mucositis prophylaxis: blinded study drug
Melphalan 200 mg / m² d -2	Tumor-specific treatment: conditioning before autologous peripheral stem cell transplantation
Granisetron 1 mg i.v. d -2, -1, 0 Dexamethasone 8 mg i.v.	Antiemetic prophylaxis during HD chemotherapy and transplantation
Filgrastim 1 x 30 million I.E.	Shortening of the neutropenic phase of stimulation and regeneration of granulopoiesis

Multiple myeloma (plasmocytoma) with FUO and mucositis after autologous stem cell transplantation

Analysis and Plan **Effectiveness of tumor therapy**	**Analysis / assessment**	**Plan / Consulting**
	• Fever of unknown origin (FUO) Despite antibiotic prophylaxis with ciprofloxacin, the patient developed fever on day 5 after transplantation. A clinical evidence of infection (catheter infection, etc.) was not present, a pathogen detection was also not possible (FUO). Despite initiation of empirical therapy with imipenem / cilastin the fever continued. In the case of fever in neutropenia a bacterial infection must be addressed first, because it can quickly become life threatening, not just in immunocompetent high-risk patients	The secondary treatment must therefore fill gaps in the current therapy and widen the bacterial spectrum. The in-house guidelines provides for first additional use of amikacin against gram-negative pathogens. Against gram-positive pathogens if the infection continues, the use of vancomycin should be considered. The empirical antibiotic therapy according to the in-house guideline initially added the minoglycoside amikacin. Dosage: Amikacin 2 x 500 mg i.v. As usual for other aminoglycoside antibiotics, the serum level has been monitored and adjusted. This toxicity can be avoided and optimal effectiveness can be reached. At response the therapy should be continued until the granulocyte count is › 1000/µl and the patient is afebrile. In case of persistent fever or worsening of clinical status further escalation in antibiotic and antifungal must take place.
	• Mucositis WHO grade IV • persistent nausea at opiate therapy The mucositis is a much feared side effect of cytotoxic therapy. In mucositis o the number of febrile days often increases. Especially in neutropenic patients the inflamed mucous membrane provides entrance gates for pathogens, so that it can lead to serious infectious complications. It also leads to a significant impairment of quality of life of patients. Particularly common is mucositis after high-dose therapies. There is a clear correlation between neutropenia and mucositis.	Pain management. Because of ocurring morphine intolerance another potent opioid has to be used. The patient is given piritramide (Dipidolor®) continuously via a perfusor syringe pump. initial dose piritramide 1 mg / h i.v. as a continuous infusion The proposed dose should be increased until adequate pain relief. If there is no nausea, the administration of metoclopramide can be dropped.

Multiple myeloma (plasmocytoma) with FUO and mucositis after autologous stem cell transplantation

	Despite appropriate oral care and mucositis prophylaxis the patient developed a mucositis WHO grade IV which is characterized by severe ulceration such that no oral intake of food and medicine is not longer possible and a continuous intravenous pain therapy is necessary. A causal prophylaxis and treatment of mucositis is not currently available with the exception of palifermin. Palifermin is a recombinant human ceratinocyte growth factor, which is approved for reducing the duration, frequency and severity of oral mucositis in autologous stem cell transplantation patients with hematological malignant disease. Long-term data are not available in sufficient quantity. Through already taken preventive activities, the risk of secondary complications is minimized. Chlorhexidine mouthwash should be discontinued as chlorhexidine, based on clinical data, has its place in the mucositis prophylaxis, but not in the mucositis therapy.	As an additional mouthwash to povidone-iodine (Betaisodona® antiseptic mouthwash) and amphotericin B (Ampho-Moronal® suspension), the patient receives also a local anesthetic lidocaine mouthwash (Viscous Xylocaine® 2%). Xylocaine Viscous 2% 10 ml rinse and gargle every 2 h (maximum 90ml/24h) The solution should be spread over the entire surface of the mouth and throat and act at least 1 minute. The application should take place before the other prophylactic / therapeutic activities. This additional pain relief drug triggers these activities, and increases the adherence of the patient. Chlorhexidine mouthwash is issued.
Control parameters	Laboratory values: normal: creatinine, sodium, potassium, calcium, ALAT, ASAT, GGT Day 5 after transplantation: - hemoglobin: 8.1 g / dl (14 - 18 g / dl) - erythrocytes 2.61 Mill / mm ³ (4.6-6.2 Mill / mm ³) - platelet 15000/mm ³ (150T – 400 T/mm ³) - leukocytes 100/µl (4.8 T – 10 T/mm ³)	