Fulminating septic shock from Clostridium perfringens in an early breast cancer patient with severe myalgia after docetaxel treatment

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Abstract

Anaerobic bacteraemia could be a life-threatening condition in neutropenic patients receiving chemotherapy. Taxane therapy is associated with necrotising inflammation of the caecum (named also typhlitis) that could be a potential source for bacteraemia. We report the case of a sudden onset of septic shock by Clostridium perfringens in a young patient treated with docetaxel as adjuvant chemotherapy for early breast cancer. A mini-review of the literature has been performed.

Introduction

Adjuvant chemotherapy (CT) is the mainstay of high risk breast cancer (BC) treatment.[1] Anthracyclines are the drugs of choice in this setting. Nevertheless taxanes can be added both as sequential and concomitant treatment. In particular Docetaxel has demonstrated activity and efficacy in several phase II and III clinical trials across the years.[1] In addition to its therapeutic efficacy, docetaxel has an acceptable tolerability profile: haematologic toxicities are the most common related side effect,[1] followed by alopecia, sensitive neuropathy, gastrointestinal symptoms and hypersensitivity reactions. Among haematologic toxicities, both severe neutropenia and febrile neutropenia might rarely be life-threatening conditions. Anaerobic bacteraemias and enterocolitis are a rare but possible complication of CT-induced neutropenia.[2-5] Here we report a case of fulminating septic shock from Clostridium Perfringens in an early breast cancer patient after docetaxel treatment.

Case Report

A 40-year-old female patient was diagnosed with infiltrating ductal carcinoma of the right breast (pT1b N1a M0, G3, ER=90%, PgR=80%, Ki-67=8%, HER2 not over expressed). No relevant comorbidities were reported in anamnesis. She therefore underwent quadrantectomy and 50 days later she started adjuvant CT with 3 courses of FEC100 q21 followed by 3 courses of docetaxel 100 mg/sqm q21. Adjuvant radiotherapy was planned at the end of the chemotherapic treatment. Eleven days after the first dose of docetaxel, she presented at our Emergency Clinic with fever (T max= 39°C), backache and leg pain lasting from about 12 hours. No other symptoms possibly related to CT toxicities were detected; she looked to be in a good general condition with performance status ECOG 0. At physical examination body temperature was 37.2°C, blood pressure=120/80, heart rate=78/min and SpO2=98%; there was a severe tenderness of both legs, with a rapidly worsening myalgia. Neither other signs at thoracic and abdominal examination, nor neurological deficit were evident. Blood tests showed mild neutropenia (1890/uL), moderate anaemia, normal renal function, hyperglycaemia and a mild liver dysfunction. Pain was not responsive to nonsteroidal anti-inflammatory drugs (NSAIDs) and morphine; when body temperature rose to 37.9°C haemocultures were executed. General condition rapidly worsened and emergency care was required to support circulatory and respiratory functions. After 2 hours blood test were repeated and showed severe neutropenia (340/uL), hypercreatinemia, metabolic acidosis, hyponatremia, hyperkalemia, decreased liver function, increase in creatine phosphokinase (CPK), myoglobin and troponin I level. Four hours after the access to our clinics the patient was dead. Differential diagnosis was made among septic shock, pulmonary embolism, aortic dissection, rabdomiolysis or chemotherapy toxicity. All haemocultures resulted negative. Post mortem examination revealed skin maceration at lower extremities, regressive changes in left ventricular myocardial wall and in the liver parenchyma with histological evidence of gaseous bullae and gram positive bacilli in myocardium, liver and kidney at interstitial and vascular level, without any inflammatory reaction. The final diagnosis was septic shock by Clostridium perfrigens.

Discussion

Anaerobic bacteraemia account for 0.5-9% of all positive cultures in hospitals. A retrospective analysis of anaerobic bacteraemia in cancer patients at the Gustave Roussy hospital was made by Zahar *et al.*[2] Forty-five patients with haematological or solid malignancies presented with bacteraemia and blood cultures positive for anaerobic bacteria (0.6% of all positive blood cultures). The median time between CT administration and bacteraemia was 17 days (8-26 days). The majority of anaerobic bacteraemia were caused by *Bacteroides* spp. (66%) or by Gram positive anaerobes (31%). Among Gram positive anaerobic bacteraemia Clostridium perfringens was the most frequent pathogen (16%). In this series, the gastrointestinal tract was the most frequent source of anaerobic bacteraemia (49%) while the site of primary infection was unknown in 17,7%. The overall mortality rate was 42%, in particular 63% for the patients who never received adequate antibiotic treatment, 47% for those who switched to adequate antimicrobics when blood cultures were available, and 14% for the patients who received adequate antibiobiotic treatment from the outset.

Risk factors for anaerobic bacteraemia in cancer patients include mucositis (disruption of mucosal barrier in the gastrointestinal tract), haematological malignancies, a prior treatment with quinolones, broad-spectrum antibiotics, and surgery. Among anaerobic bacteraemia, clostridial infection could present with non-specific symptoms (fever, hypotension, local crepitation, abdominal pain and distension). In the past, several cases of clostridial septicaemia were reported in children receiving CT for lymphoproliferative disorders as lymphoblastic leukaemia, B-cell non-Hodgkin lymphoma and histiocytosis X. All cases presented with symptoms like watery diarrhoea, abdominal pain, fever and granulocytopenia; septicaemia was never fatal.[3,4]

Necrotising inflammation of the cecum (also named typhlitis) due to taxanes is a potential source of bacteraemia. Five cases of

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acute neutropenic enterocolitis complicating the taxane-based CT have been described; two cases evolved in septic shock, both of them occurred 7-10 days after the administration of CT5. One case of septic shock has been reported in a patient receiving docetaxel for a colangiocarcinoma[6] as well as in 3 patients treated with docetaxel for advanced or recurrent gastric cancer.[7,8] In a review of clinical trials with docetaxel for metastatic breast cancer, 6 cases of ischemic colitis were identified, two of them were fatal.[9]

Grade 4 neutropenia (ANC<500/uL) and febrile neutropenia occur respectively in about 75 and 11% of patients treated with docetaxel for early breast cancer (EBC) in adjuvant setting.[1] In the Breast Cancer International Research Group (BCIRG) 001 trial, docetaxel 75 mg/m^2 in combination with doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC regimen) showed to reduce the risk of breast cancer recurrence when compared with fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) in EBC.[10] In this trial, prophylaxis with ciprofloxacin was required during TAC. Febrile neutropenia was significantly more common in patients treated with TAC than in those treated with FAC (24% vs 2.4%; P<0.05), although the incidence of grade 3/4 infection was low in both groups (3.1 and 1.5% respectively) and no death was due to infection.[11] In The Spanish Breast Cancer Research Group (GEICAM) trial, which has a design similar to BCIRG 001, after a protocol amendment due to high neutropenic complications, in patients receiving TAC primary prophylaxis (PP) with Granulocyte – colony stimulating factors (GCSF) and ciprofloxacin were mandatory. The addition of GCSF PP resulted in reduction of neutropenic fever and lead to an improvement in health-related quality of life.[12] In a non-anthracycline containing adjuvant regimen, the association of docetaxel 75 mg/m^2 with cyclophosphamide 600 mg/m^2 was associated with more fever and neutropenia compared with standard dose doxorubicin + cyclophosphamide (5% *vs* 2.5%) and one case of death with sepsis and neutropenia was reported in the docetaxel arm.[13] In Plc Advant Controller System (PACS) 01 phase III randomised trial in EBC [Fluorouracil-epirubicin-cyclophosphamide (FEC) for six cycles vs. FEC for three cycles followed by three cycles with docetaxel 100 mg/m^2] the incidence of neutropenia G3-4 was higher in FEC arm (33.6% *vs* 28.1%), while febrile neutropenia rate was higher in the taxane arm (11.2% *vs* 8.4%). In this trial GCSF PP was not allowed.[14]

The European Society for Medical Oncology (ESMO) recommends GCSF PP for CT regimens with 20% or more risk of febrile neutropenia or in which dose reduction is deemed detrimental to the outcome.[15] In the National Comprehensive Cancer Network (NCCN) guidelines GCSF PP is not recommended for CT regimens with a risk of febrile neutropenia less than 10% whereas it is recommended in patients with risk >20%. Individual patient, disease characteristics and goal of the treatment should be taken into consideration in the case of CT regimens with risk between 10 and 20%.[16]

In our study case, the patient presented with severe myalgia in the inferior arms, that was unresponsive to major opioids and that could be related to a clostridium infection. However, myalgia is a common taxane-related side effect (42% in patients treated with FEC-D, 26.7% in patients treated with TAC), usually reversible with conventional analgesics. Myalgia G3-4 occurs only in 5% of patients treated with FEC-D, the percentage is lower when patients are treated with TAC (0.8%).[10,17] This case-study outlines the relevance of potentially life-threatening infections during docetaxel-based chemotherapy. Physicians should take into account the risk of anaerobic sepsis in neutropenic patients with fever and severe myalgia. It could be hypothesised that the source of Clostridium perfringens bacteraemia in this patient was the gastrointestinal tract. As discussed above, neutropenic enterocolitis is a potentially fatal complication of taxane-based chemotherapy. It should be taken into consideration that even bacterial translocation through damaged intestinal barrier (e.g. during chemotherapy-related mucositis) can be responsible for sepsis in neutropenic patients.[18] Presentation with acute onset and rapid clinical deterioration lead to a difficult diagnosis and treatment of this septic shock.

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