Fatal sepsis after thalidomide/dexamethasone treatment in two patients with multiple myeloma

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Thalidomide exerts remarkable antineoplastic activity in patients with newly diagnosed or progressive/relapsed multiple myeloma (MM).[1,2] It is generally well tolerated, leading to mild or moderate adverse effects such as constipation, weakness or fatigue in only about one third of patients.[1] In combination with dexamethasone or chemotherapeutic agents, which yield even higher anti-myeloma activity, more severe adverse effects such as thromboembolic events and toxic epidermal lysis were described.[3,4] Here we report two myeloma patients with fatal sepsis after combined thalidomide/dexamethasone treatment. The first patient, a 70-year old Caucasian male, with a stage IIIA IgG-kappa myeloma was included in a randomized prospective study of the International Myeloma Trial Group comparing thalidomide/dexamethasone versus melphalan/prednisone as first-line treatment. Medical history revealed an advanced malignant melanoma, which was successfully treated with surgery and radiotherapy seven years prior to the diagnosis of MM and mild chronic bronchitis. At initiation of therapy with 200mg thalidomide daily plus 40 mg dexamethasone once daily for the first four days the patient was in good health with no signs of infection, cardiac or acute pulmonary disease. Blood tests revealed mild leukopenia (2,500 cells/μL; 68% neutrophils, 22% lymphocytes, 1% basophils, 9% monocytes), anemia (hemoglobin 10.3g/dL), mild renal insufficiency (creatinine 1.4 mg/dL) and hyperuricemia, but no immunoglobulin deficiency. On day 7 the patient presented in our emergency department with fever (up to 39°C) for two days, productive cough and increasing dyspnea. Physical examination revealed arrhythmic tachycardia, tachypnea and cyanosis. Chest X-ray showed signs of congestive heart failure but no pulmonary infiltrates. Blood tests revealed leukocytosis (12,000/μL), anemia (hemoglobin 10.3 g/dL), thrombocytopenia (67,000/μL), increasing creatinine levels (2.2 mg/dL) and signs of disseminated intravascular coagulation. Treatment with thalidomide was discontinued and immediate broad-spectrum antimicrobial therapy with ceftazidime and fluconazole was initiated. As blood cultures were positive for Staphylococcus aureus, antibacterial therapy was changed to flucloxacillin and levofloxacin. However, the patient's condition deteriorated. On day 9 a chest X-ray showed pulmonary infiltrates and on the next day overt therapy-refractory septic shock with multi-organ-failure occurred. The patient died on day 11 after initiation of thalidomide and dexamethasone. The second patient, a 59-year old Caucasian female, was diagnosed with stage IIIA IgG-kappa MM in April 2001. Treatment with four cycles of VAD (vincristine 2 mg, adriblastine 9 mg/m2 and dexamethasone 12x40 mg) and autologous peripheral blood stem cell transplantation after melphalan conditioning (200 mg/m^2) resulted in partial remission of MM. Despite maintenance therapy with interferon alpha the disease progressed and therapy with thalidomide and dexamethasone was initiated in June 2002. At this time the patient showed anemia (hemoglobin 10.3g/dL), thrombocytopenia (105,000/μL) and secondary hypogammaglobulinemia but was otherwise in good health with no signs of infection, cardiac or pulmonary disease. Thalidomide and dexamethasone were given as described above. On day 15 after start of therapy, the patient reported mild fatigue but was otherwise without symptoms. Physical examination was normal as were routine serum chemistry tests. Hemoglobin levels fell to 9.9 g/dL, but platelet counts rose to 135,000/μL. Serum paraprotein levels already showed a marked decline. Therefore, thalidomide was continued and a second cycle of dexamethasone for four days was administered. Additionally, human recombinant erythropoietin therapy was initiated. On day 19 the patient developed a cough and fever of up to 40°C, which was treated with antipyretics by herself. On the next day she was prescribed cefuroxime by her family physician. Since dyspnea developed on day 21 and her condition increasingly deteriorated, she was referred to the nearest hospital, where a diagnosis of sepsis due to pneumonia with acute renal failure was made. Thalidomide was stopped and despite imipenem and symptomatic treatment with fluid substitution septic shock and pulmonary insufficiency developed. After intubation and stabilization of the blood pressure with noradrenaline the patient was referred to the intensive care unit of our department. Laboratory tests revealed pancytopenia (leucocytes 660/μL, hemoglobin 8.6g/dL, thrombocytes 44,000/μL), acute renal failure with a creatinine of 4.6mg/dL, hyperkalemia (6.6mmol/L), severe lactate acidosis (pH 7.08; lactate 21,6mmol/L) and disseminated intravascular coagulation. Chest X-ray showed left-sided pleural effusion, focal infiltrates in the left lung and global cardiac enlargement. Microbiological cultures of the bronchoalveolar lavage yielded Pseudomonas aeruginosa. Despite intensive care management the patient died five hours after arrival on day 21 after initiation of thalidomide and dexamethasone. Thalidomide is a drug with anti-angiogenic, anti-inflammatory, and immunomodulatory properties.[5] Among its so far characterized mechanisms of action, inhibition of production of TNF-alpha by activated monocytes is in part responsible for its clinical effects.[6] This mechanism may have been crucial with respect to the fatal outcome in the patients described above.TNF-alpha is an important mediator of local inflammation and is vital in keeping infections localized: genetically TNF-receptor deficient mice fail to control infection by bacteria.[7] This is also in line with reports of severe infections with occasional fatal outcomes during use of anti-TNF-alpha antibodies or recombinant soluble TNF-alpha receptors for treatment of rheumatoid arthritis.[8,9] Since dexamethasone also decreases TNF-alpha production, and the combination of both is additive,[10] this combination therapy may have markedly increased susceptibility as well as vulnerability to overwhelming bacterial infections. Although the contribution of thalidomide to the fatal infections in our patients is not proven, close monitoring of infections in patients treated with this otherwise precious drug is very strongly recommended, particularly when it is combined with dexamethasone.

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