Intrapleural instillation of rituximab for the treatment of malignant pleural effusions in NHL

A patient with CD20+ leukaemic lymphoplasmacytic Non-Hodgkin´s lymphoma (NHL) presented with bilateral malignant pleural effusions. Systemic chemotherapy, repeated percutaneous drainage and bilateral continous chest tube drainage were unable to control the effusions. Rituximab was instilled in a dose-escalating manner via the chest tubes into both pleural spaces, within two weeks the effusions resolved, and the patient has stayed free of symptoms for eight months ongoing. Rituximab may be a promising novel treatment option for malignant effusions in CD20+ NHL.

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Malignant pleural effusions are a common clinical problem in patients with neoplastic disease. Approximately 10% of malignant pleural effusions are caused by Non-Hodgkin´s lymphoma (NHL).[1] The effusions may be due to direct tumor infiltration of the parietal or visceral pleura and/or obstruction of the lymphatic drainage by tumor infiltration or enlarged mediastinal lymph nodes. Systemic chemotherapy can be effective in patients with symptomatic malignant pleural effusions, however, when systemic treatment is or has become ineffective, local therapy such as pleurodesis should be considered.[1] Talc is now increasingly recommended but historically many other chemical agents have been instilled into the pleural space in an attempt to produce pleurodesis and have shown some effectiveness in controlling effusions, including doxycycline, bleomycin, biologic agents and others.[1] We report for the first time on successful treatment of bilateral malignant pleural effusions in a patient with NHL by instillation of anti-CD20 monoclonal antibody (rituximab) into the pleural cavity.

Case report

In January 2002 a 57-year-old male was diagnosed with CD20+ leukaemic lymphoplasmacytic NHL, no therapy was initiated. In July 2003 because of disease progression (increasing leukocytosis and lymphadenopathy) the patient received one cycle of oral fludarabine (40 mg/m^2/day for 5 days). At this time, also small bilateral pleural effusions (partially encapsulated on the left side) were noted. Regardless of chemotherapy, the effusions were increasing, diagnostic thoracentesis three weeks after chemotherapy demonstrated a bloody, exudative effusion with leucocytosis of 30.5×10^9/L and failed to isolate any infectious pathogen. Cytology and immunophenotyping revealed 85% CD20+ lymphoma cells, confirming the malignant nature of the effusion. The symptoms of the patient did not resolve despite repeated percutaneous drainage of large volumes (up to 2000 mL). Thus, bilateral continous chest tube drainage was performed. However, after five days the amount of pleural fluid drained per day did not fall below 200 mL. For additional treatment and after informed consent was given by the patient, rituximab was instilled in a dose-escalating manner in an operating room setting via the chest tubes into both pleural spaces. Under standard premedication with dimetinden and mefenamin, a test-dose of 50 mg rituximab in a solution of 50 mL of sterile saline were instilled as a bolus on day one into the right pleural cavity, followed by a 200 mg bolus on day two on the left side and a 400 mg bolus on day three again on the right side (both in a volume of 100 mLover 5 minutes). After each instillation, the chest tube was clamped for 6 hours and was subsequently reconnected to -20 cm H_2O suction. The therapy was tolerated well without any side effects and, initially, a rapid decrease of the peripheral blood (PB) lymphoma cell counts was observed. However, after three days, in absence of any signs of infection, PB lymphoma cells were rising again, reaching a threefold increase after 6 days (Figure 1). At this time, both chest tube drainages still yielded more than 200 mL pleural fluid per day. Surprisingly, without any further therapy, the PB lymphoma cell counts began to decrease and, simultaneously, the daily output of the chest drainages of both sides fell to below 50 mL. Finally both drainages could be removed. During a follow up of 6 months the patient was asymptomatic, he received 4 courses of intravenous rituximab consolidation therapy. Pleural sonography showed complete disappearance of the effusions on the right side, while a small encapsulated effusion (~ 3 cm diameter) persisted on the left side, the pre- and post-treatment chest x-rays are shown in Figure 2. Despite increasing splenomegaly in April 2004 no recurrence of the pleural effusions was noted.

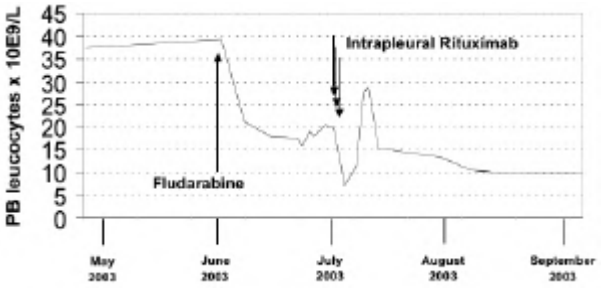

Figure 1. Peripheral blood (PB) counts between Fludarabine chemotherapy and intrapleural instillation of rituximab. Differential blood counts revealed that all changes were due to a rise or fall of the PB lymphoma cells. The sharp decrease of the PB lymphoma cells after intrapleural rituximab therapy indicates that significant amounts of the antibody reached the circulation in an active form. The consequent increase occurred in absence of any signs of infection and resolved without any further therapy.

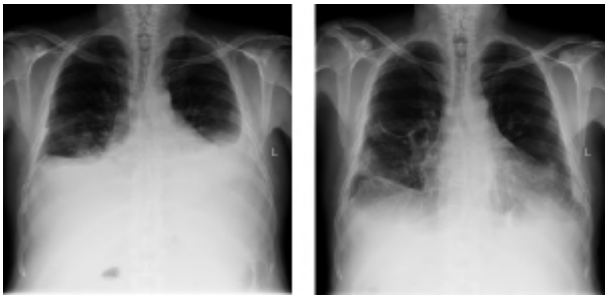

Figure 2. Chest X-rays before and after intrapleural instillation of rituximab.

Discussion

Rituximab is a chimeric monoclonal antibody that binds to the CD20 antigen, which is expressed on 95% of B-cell lymphoma cells and on normal B-cells.[2] The efficacy and safety of rituximab in the treatment of most types of CD20+ NHL, either as a single agent or in combination with chemotherapy, were established in a variety of studies.[2] Rituximab has been administered almost exclusively slowly via the intravenous route, data relating to the safe-

ty, efficacy, and pharmacokinetics of other routes of administration are incomplete.[3-5] Our observations indicate that the rapid pleural instillation of even large doses can be tolerated without any adverse effects and may be effective in controlling malignant effusions. Rituximab binding to CD20 induces several mechanisms of cell destruction including direct signaling of apoptosis, complement activation and antibody dependent cellular cytotoxicity.[2] Although the serum levels of rituximab were not measured after intrapleural antibody instillation, the constant decrease of the PB lymphoma cells clearly demonstrates that significant amounts of the antibody were resorbed and reached the circulation in an active form. Thus, the therapeutic effect of rituximab in this case may be due to several factors including destruction of infiltrating lymphoma cells in the visceral/parietal pleura or pleural cavity and/or tumor-cell clearance of the pleural lymphatic drainage vessels. The temporary rebound-like increase in the PB lymphoma cells after rituximab instillation (Figure 1) remains somehow unclear, but might be explained by a release of (preapoptotic) lymphoma cells captured in the pleural compartment into the circulation.

In summary, we report a promising novel treatment option for malignant effusions in CD20+ NHL. Rituximab was tolerated well and induced a long-lasting remission of the effusions, despite disease progression on other sites. Thus, the efficacy of the monoclonal antibody in this clinical setting should be investigated in additional cases.

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