OUTPATIENT TREATMENT OF MALIGNANT PLEURAL EFFUSIONS RELATED TO METASTATIC BREAST AND OVARIAN CANCER WITH INTRAPLEURAL INSTALLATION OF THE TRIFUNCTIONAL ANTIBODY CATUMAXOMAB

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BACKGROUND

Pleural effusion (PE) is a frequent complication of various malignancies with metastatic spread to the pleural cavity. Malignancies most frequently associated with PE are carcinomas of the lung, breast, ovary, and malignant mesothelioma. Major symptoms associated with PE are dyspnea, asthenia, fatigue, and pain. Standard of care in the treatment of PE comprises serial punctures, insertion of a permanent pleural drain, and pleurodesis with sclerosants like tetracycl, or silver nitrate. Although low toxic in general, chemical pleurodesis requires hospitalization and admission of the patient (pts) to an intensive-care unit. This is due to the fact that complete evacuation of the pleural cavity by using a vacuum drainage system is mandatory prior to the installation of a sclerosant. Intrapleural (IP) instillation of sclerosants cytostatics such as bleomycin, mitomycin C, mitomycin, tetracycline or doxycycline can be performed more easily in outpatients but may also be less effective in regard to the puncture-free interval (PuFI).

Epithelial tumours producing malign effusions often express the epithelial cell adhesion molecule (EpCAM). Catumaxomab is a trifunctional monoclonal antibody (anti-EpCAM x anti-CD3) approved in 2009 for the intrapleural treatment of malignant ascites related to EpCAM-positive epithelial neoplasms. Catumaxomab has been found to be active in the treatment of malignant ascites in several phase II-IV trials (Heiss et al., 2010, Kurbacher et al., 2013). Intrapleural catumaxomab therapy normally requires 4 subsequent instillations at increasing dosages (i.e. 10, 30, 50, and 150 µg absolute dose) over a 14 days period. For IP treatment, serial instillations mostly appear to be inappropriate apart from a very few pts who have a permanent pleura catheter inserted. Successful immunotherapies require the application of an antibody at its saturation level which for catumaxomab by may be reached at 50 or even 20 µg. We hereby report on a series of intensively pretreated outpatients suffering from PE related to metastatic breast (MBC) or recurrent epithelial ovarian cancer (ROC) treated with IP catumaxomab in a routine clinical setting.

METHODS

A total of 12 pts with PE (MBC n=7, ROC n=5) were treated with IP catumaxomab. Six MBC pts had invasive lobular carcinoma, the remainder had estrogen receptor-negative, HER2-positive invasive ductal adenocarcinoma. All five ROC pts suffered from high-grade papillary serous adenocarcinoma (type II ovarian carcinoma). EpCAM-positivity was confirmed by immunohistochemistry in all cases. All pts were heavily pretreated having failed a median of 6 (3-12) prior systemic treatments. Baseline characteristics of the pts are summarized in Table 1. In all pts, ultrasound-guided pleural puncture was performed as outpatient setting. In these pts, catumaxomab was given at an absolute dose of 50 µg administered as a 10 µl IP injection. In one pt, this procedure was repeated after 25 days. One pt was referred to our institution for further treatment after implantation of a permanent IP catheter. In this instance, catumaxomab treatment was given according to the intrapleural scheme at 4 increasing doses (i.e. 10, 20, 50, and 150 µg) instilled over 3 hours for a 14 days treatment period. Standard premedication included IV administration of metamizole (1 g) and granisetron (3 mg). After IP instillation, the analgesic/antipyretic and antieptic treatments were continued for 3 consecutive days by using oral or subcutaneous formulations of the particular drugs. In one pt experiencing hypotension during IV metamizole, antieptic treatment was changed to 1 g of paracetamol. In patient #10 with known severe allergy towards all kinds of established non-steroidal pain-killers, we abstained from administering antieptics. In this particular case, analgesic premedication consisted of IV paracetamol at 50 µg. Adverse effects were recorded according to the CTCAE 4.03 scale. The PuFI was defined as the interval between the start of IP catumaxomab and first subsequent pleural puncture due to symptomatic PE. OS was calculated from the start of catumaxomab and death of any reason or loss to follow-up. The puncture-free survival was calculated from start of IP catumaxomab and next puncture, death or loss to follow-up, whatever was the first to occur.

RESULTS

Treatment results are summarized in Table 2. Outpatient IP catumaxomab was generally well tolerated. As with intrapleural instillation, major side effects can be considered cytolytic-related and comprised fever, pain, hypotension, and dyspnœa. Side effects were well controlled by routinely administered supportive medication including both antipyretics and antieptics and were never exceeded CTC-AE grade II with the exception of one case in which the administration of non-steroids had to be avoided (patient #10). This patient was also the only one needing hospitalization secondary to IP due to fever and local pain. Only 3 pts developed symptomatic PE after IP catumaxomab treatment and needed subsequent punctures. All but 4 pts were able to undergo subsequent antineoplastic treatment following IP catumaxomab. Recently 4 pts are still alive. Median PuFI is 112 days and median OS is 134 days (Figure 1).

CONCLUSIONS

Outpatient IP catumaxomab feasible in this intensively pretreated group of patients with either MBC or ROC.

IP catumaxomab was generally well tolerated. Relevant side effects were recorded in only 5 patients and rarely exceeded CTC-AE grade II.

The quality of adverse effects were similar to that seen with intrapleural catumaxomab therapy for malignant ascites.

Toxicity was manageable even in relatively “frail” patients with a low initial performance status.

IPL catumaxomab, although given as a 50 µg single shot in most patients, could effectively control symptomatic PE.

Eight out of twelve patients (66.7%), were able to undergo a subsequent symptotic antieptic IP treatment.

A median PuFI of 112 days and a median OS 134 demonstrated a clinically meaningful activity of IPL catumaxomab.

IPL catumaxomab offers a new, low-toxic and easy-to-administer option in patients with symptomatic PE related to MBC or ROC which, in contrast to pleurodesis with talc or silver nitrate, can be given in an outpatient setting in the vast majority of patients.