RESEARCH ARTICLE

Intrapleural or Intraperitoneal Lobaplatin for Treatment of Patients with Malignant Pleural Effusion or Ascites

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Abstract

Aims: To explore efficacy and side effects of intrapleural or intraperitoneal lobaplatin for treating patients with malignant pleural or peritoneal effusions. Methods: Patients in Jiangsu Cancer Hospital and Research Institute with cytologically confirmed solid tumors complicated with malignant pleural effusion or ascites were enrolled into this study. Lobaplatin (20-30 mg/m^2) was intrapleurally or intraperitoneally infused for patients with malignant pleural effusion or ascites. Results: From 2012 to 2013, intrapleural or intraperitonea lobaplatin was administered for patients with colorectal or uterus cancer who were previous treated for malignant pleural effusion or ascites. Partial response was achieved for them. Main side effects were nausea/vomiting, and bone marrow suppression. No treatment related deaths occurred. Conclusion: Intrapleural or intraperitoneal infusion of lobaplatin is a safe treatment for patients with malignant pleural effusion or ascites, and the treatment efficacy is encouraging.

Keywords: Lobaplatin - malignant pleural effusion - ascites - gastric cancer - colorectal cancer

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Introduction

Malignant pleural or peritoneal effusion (MPE) is an abnormal accumulation of fluid in pleural or peritoneal cavity associated with several malignancies. MPE is considered to be the first clinical manifestation of malignancy as well as the first sign of recurrent cancer. The prognosis remains poor with a median survival after MPE diagnosis between 4 to 9 months (Bielsa et al., 2008). In general, adenocarcinoma is the most common histological type responsible for MPE (Awasthi et al., 2007). The malignancies frequently associated with MPE are lung cancer (37%), breast cancer (25%), lymphoma (10%), ovarian cancer (5%), stomach cancer (2%), unknown primary (7%), and other causes (14%) (Mark, 2001). In 5-10% of patients with a MPE, no primary tumor is identified (Johnston, 1985). Pleural malignancies may arise from tumor involvement of the visceral pleura, direct extension from neighboring structures, or hematogenous or lymphatic spread to parietal pleura; but, the exact mechanism of malignant pleural fluid accumulation is not entirely understood (Wheate et al., 2010). Ascites was the initial presenting sign or symptom in 54%of patients. More than 95% of patients with malignant ascites also had measurable metastatic disease in the peritoneum (90%), liver (27%), bone (12%), and lung (8%). The cancers most commonly associated to ascites are ovarian (37%), pancreatic biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%) (Ayantunde, 2007). Intracavitary administration of anticancer drugs is a common method for treating malignant pleural effusion or ascites. Platinums are the common used drugs, cisplatin and carboplatin have been reported (Bogholo et al., 1991; Esposito et al., 1994). We hypothesize that intrapleural lobaplatin is also an effective option for patients with malignant pleural effusion or ascites.

Materials and Methods

Patient selection

Patients histologically confirmed with solid tumor and complicated with malignant pleural effusion or ascites in Jiangsu Cancer Hospital & Research Institution were eligible for this study. Other eligibility criteria required patients to sign an informed consent before treatment; to expose to long term chemotherapy or supportive care; to have a score of karnofsky performance status ≥ 70; to be 25 to 75 years of age. Other eligibility criteria included: adequate hematological (white blood cell count > 3.0×10^9 and platelet count > 150×10^9), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine level < 1.5 times the upper

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normal limit); patients were excluded from this study if they failed to complete intrapleural or intraperitoneal chemotherapy, or with any serious medical or psychiatric condition, or other malignancies. Pregnant or lactating women are also excluded from this study.

Treatment plan

Lobaplation (10-30 mg/m^2) was dissolved in 5% glucose and infused intrapleurally or intraperitoneally after thoracentesis or abdominocentesis.

Evaluation

The response was evaluated by ultrasound based on the findings of posteroanterior 4 weeks after treatment. The response criteria used were as follows: a complete response (CR) when no pleural effusion or ascites was observed; a partial response (PR) when pleural effusion or ascites was significantly decreased; and no response (NR) when effusion was larger than that defined by PR. An ultrasound in responding patients was taken at least every month in order to monitor the condition of the controlled effusion. The response and duration of response were determined by an oncologic examination group. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (version 2.0) (National Cancer Institute, 1998).

Research experience

We have much experience in conducting medical research, and have published results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

Li, is a 44-year-old male patient (registration number of Jiangsu Cancer Hospital & Research Institute, 227216). In July 2012, he presented with upper right abdomen pain. Computer tomograph (CT)/magnetic resonance (MRI) and PET-CT showed multiple liver lesions and multiple nodular infiltrations in left and right upper lung, and pleural effusion in right side of chest. Colonoscopy discovered a tumor 60 cm from anus, histologically confirmed adenocarcinoma. Histological diagnosis after liver biopsy also suggested adenocarcinoma. The patient received systemic chemotherapy, consisting S-1 two tablet a day for two weeks + oxaliplatin 100mg intravenously (i.v.) on day 1, and day 8 (d1, 8). Then treatment was adjusted to irinotecan 100mg i.v. d1,8+ oxaliplatin 100mg i.v. on d1,8+FT-207 0.8g i.v. d1-3,d8-9, because of treatment-related liver impairment. After two cycles, CT examination suggested: multiple liver metastases lesions, a soft tissue mass in left abdomen and pleural effusion. On March 12 of 2013, Lobaplation 30mg was dissolved in 50 ml 5% glucose and infused intrapleurally after thoracentesis.

Another patient is Mao, a 45-year-old female (registration number of Jiangsu Cancer Hospital & Research Institute, 231813). In November 2012, she presented with abdominal discomfort. Ultrasound showed diffuse lesions in uterus, cervical hypertrophy with inhomogenous internal echoes, a mixed mass (size 6.4*5.7cm) in right adnexa, massive intraperitoneal effusion. Pathologic diagnosis is low differentiated adenocarcinoma. CT showed a cystic lesion in right adnexa, mass fluid in abdomen pelvic cavity, gastric wall thickening in segmental body of stomach and stomach sinus carcinoma was considered. After admission, she received abdominal paracentesis and 2000 ml yellow ascites was drained. Cytological examination of ascites suggested of malignant cells. The patient received systemic chemotherapy consisting docetaxel 60mg d1,d8 +cisplatin 20mg d1-5 + S-1 50 mg bid d1-14. After two cycles, CT examination demonstrated ascites increased. We adjusted chemotherapy that was docetaxel 60mg d2, d8 + pemetrexed 0.8g d4, then Lobaplation 30mg dissolved in 50 ml 5% glucose and infused intraperitoneally after abdominocentesis.

Adverse events and Response

After follow-up, no grade 4 haematological or nonhaematological toxicities were observed. For two patients, pleural effusion and ascites were controlled and PR was achieved.

Discussion

The management of malignant effusion depends on its etiology, general condition of patient, and expected survival. Locoregional therapy is important in this setting. Agents administered intrapleurally for treating malignant pleural effusion include non- cytotoxic or cytotoxic medications. Non- cytotoxic drugs include those with a sclerosing effect that produces pleurodesis, and most frequently used is talc in the United States (Hausheer, 1985), tetracycline or doxycycline in the United Kingdom (Putnam et al., 1999) and OK432, which is prepared from a substrain of Streptococcuspyrogenes A3, in Japan (Saka et al., 1994). Problem of these agents, e.g., severe chest pain during pleurodesis was reported to be 17% (Hartman et al., 1993). The administration of OK432 is easily performed through a chest tube and it is reported to control over 70% of malignant pleural effusion. However, the mechanism of action for controlling effusion remains unclear. Cytotoxic agents, e.g., etoposide, mitomycin-C, doxorubicin, cisplatin etc, were also reported (Seto et al., 2006). For ascites, more cytotoxic drugs were reported, e.g, bleomycin (Ostrowski, 1986), mitoxantrone (Lee et al., 2002), 5-FU (Schilsky et al., 1990), cisplatin (Kitani et al., 2001), paclitaxel (Kitayama et al., 2010), and docetaxel (Naitoh et al., 2004). Cytotoxic drugs administered intrapleurally or intraperitoneal for the management of malignant effusion is considered more effective, however results of previous trials are still unsatisfactory. Therefore, it is urgent to develop more effective regimens to treat patients with MPE.

Lobaplatin is a third-generation platinum, delivered as a diastereomeric mixture of S, S and R, R configurations of the carrier ligand, complex with DNA alkylating activity.

It increases the expression of the c-myc gene, which is involved in oncogenesis, apoptosis and cell proliferation (Aristides et al., 1995). Compared with cisplatin, lobaplatin is considered to be less toxic, more soluble and stable in water (Voegeli, 1990; Mark, 2001). Lobaplatin demonstrates activity in preclinical tumour models and appears to be effective for tumors that failed cisplatin and carboplatin. At present, lobaplatin is approved for treating patients with chronic myelogenous leukemia, inoperable metastatic breast cancer and small cell lung cancer. Moreover, a combination of lobaplatin with vinorelbine was introduced for treating patients with late-stage non-small cell lung cancer and advanced breast cancer (Wheate et al., 2010). Currently, a combination of lobaplatin with 5-FU and leucovorin is under phase III clinical trials for treating patients with recurrent or metastatic esophageal carcinoma (Gietema et al., 1993). It is interesting to note that no alopecia, renal, neuro- toxicities are observed after lobaplatin IV injection (Gietema et al., 1993; Gietema et al., 1995; Marian et al., 1995; Welink et al., 1999). Side effects of lobaplatin include anemia, nausea and vomiting (Mross et al., 1992; Gietema et al., 1993). Thrombocytopenia is the most commonly documented dose limiting toxicity associated with lobaplatin (Gietema et al., 1995; Manegold et al., 1996; Sternberg et al., 1997; Wheate et al., 2010). However, no English reports were found that intrapleural or intraperitoneal administration of lobaplatin is a proper choice for treating patients with malignant pleural effusion or ascites. Our results suggest that intrapleural or intraperitoneal administration of lobaplatin is an effective treatment for malignant pleural effusion or ascites, and adverse sides are mild. Although this therapy is considered to be a feasible and active treatment for malignant effusion, further trials with randomized design are encouraged.

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