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Clinical progression of lobaplatin in combination chemotherapy for patients with recurrence or metastatic cancer*

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Abstract The platinum-based combination chemotherapy has become one of the major modalities in anti-cancer treatment. After the first-line chemotherapy, many patients need further chemotherapy because of recurrence or metastasis. Lobaplatin is one of the third generation platinum drugs,and this article briefly reviews the clinical progression of lobaplatin in combination chemotherapy for patients with recurrence or metastatic cancer.

Key words lobaplatin; chemotherapy; recurrence; metastasis; combination chemotherapy

Cisplatin (DDP)-based chemotherapy has had a major impact in the clinical management of cancer therapy. But severe side effects restricted the applications of DDP, which compelled scientists to exploit strategies for developing new platinum based drugs. Recent studies had showed that lobaplatin [1, 2-diaminomethylcyclobutane platinum (II) lactate, LBP] had a strong antitumor activity and did not induce any significant neurotoxicity or nephrotoxicity. It was no need of saline hyper-hydration and more soluble and stable in water. The drug resistance rate was far lower than that of DDP. LBP had limited degree of cross-resistance with DDP [1–4]. LBP acted by a mechanism similar to other platinum drugs. LBP mainly formed Pt-GG and Pt-AG intra-strand cross-links, which caused distortions of DNA and altered the normal function of DNA, such as replication or transcription process. DNA-damage induced by LBP may influence the expression of certain genes in tumour cells [2]. LBP had been approved by China Food and Drug Administration in the treatment of advanced breast cancer, small cell lung cancer (SCLC) and chronic myelogenous leukemia.

Yang *et al* [4] summarized that LBP had promising efficacy no matter in single or combination therapy in 2009, and put forward several problems: firstly, large sample, randomized controlled and multi-center clinical trials were lacking. Secondly, no studies reported phase I/II clinical trials and the standard dose of LBP of combination therapy. In the present study, we summarized the clinical progression of LBP in combination chemotherapy for patients with recurrence or metastatic cancer.

Lung cancer

SCLC

SCLC is the most aggressive among lung cancers, and the prognosis is poor. DDP plus VP-16 (EP) regimen is the standard first-line therapy and has a high efficacy. However, the majority of patients relapsed in 1 year after the first-line therapeutic regimen of EP and need further treatments.

Yang *et al* [4] reviewed 19 patients with recurrence SCLC after chemotherapy using LBP 40 mg/m^2 as the second-line treatment: 17 cases were assessable for evaluation, and resulted in two cases of stable disease (SD) and 61% of patients occurred the dose-limiting toxicity-thrombocytopenia, suggesting the potential effectiveness of LBP 40 mg/m^2 was poor and the toxicity was severe.

Xu *et al* [5] analyzed the preliminary results of 24 cases

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of SCLC using LBP 35 mg/m^2 and irinotecan 200 mg/m^2 after therapeutic regimen of EP as the first-line treatment, and results were as following: twenty-four patients were evaluable for response, in which 2 achieved complete response (CR) and 8 partial response (PR), namely the objective response rate (ORR) was 41.7%, 5 patients had SD and 9 progressive disease (PD). Thus the disease control rate (DCR) was 62.5%. The median time to progression (TTP) and overall survival (OS) was 4.3 months and 7.4 months, respectively. The 1-year survival rate was 33.3%. The main toxicity was the hematological toxicity and gastrointestinal side effects. Grade III/IV leukopenia was seen in 12 patients (50.0%), and thrombocytopenia in 5 patients (20.8%). Diarrhea was seen in 21 patients (87.5%), 14 of who were grade III/IV. One study [6] included 26 advanced cases of recurrence or progression SCLC were treated with LBP combined irinotecan-based therapy, LBP 35 mg/m^2 d1, irinotecan 200 mg/m^2 d1, in which 2 achieved CR and 8 PR, and the ORR was 42.3%. Six patients got SD, and nine patients experienced progression. Thus the DCR was 65.4%. The median progression-free survival (PFS) and OS were 4.3 months and 7.1 months, respectively. The 1-year survival rate was 31.4%. The main toxicity was the hematological toxicity and gastrointestinal side reaction. No Grade III/IV diarrhea was seen. Grade III/IV leukopenia was seen in 14 patients (53.8%), and thrombocytopenia in 12 patients (46.2%).

Wu *et al* [7] compared the efficacy, safety and OS of irinotecan and oxaliplatin (IL) regimen consisted of irinotecan combined with LBP and ironotican and carboplatin (IC) regimen consisted of irinotecan combined with carboplatibn as second-line chemotherapy for the patients with SCLC. The response rate (RR) and DCR in (IL) regimen group and IC regimen group were 54.2% (26/48), 32.6% (15/46) and 70.8% (34/48), 60.9 % (28/46), respectively. The RR in IL regimen group was higher than that in IC regimen group (P = 0.040), and the DCR in two groups did not show significant difference. The median PFS and OS in IL regimen group and IC regimen group were 3.3 months, 2.8 months and 7.1 months, 6.6 months, respectively, with no significant difference.

LBP combined with irinotecan regimen for patients with SCLC that progressed after first-line chemotherapy exerted favorable safety, prolongation of the survival time and improvement of the quality of life. But for now we still lack of large sample, multi-center clinical trials to confirm it.

Non-small cell lung cancer (NSCLC)

Many NSCLC patients are in advanced-stage disease and un-resectable when clinical diagnosed. Thus, platinum-based chemotherapy has become one of the most important methods of the treatment. Most of them need to receive second-line or above chemotherapy due to relapse or metastasis after the first-line chemotherapy, but the effects were not satisfactory.

Several studies [8–10] reported docetaxel (TXT) 75 mg/m^2, every 21 days, as second-line treatment of NSCLC was effective, and toxicity was tolerated. TXT has been approved as one of the standardized second-line chemotherapy drugs for NSCLC [11].

Wu *et al* [12] reported the efficacy and safety of second-line chemotherapy consisted of LBP combined with TXT in the patients with advanced NSCLC compared with TXT alone. In the combined regimen group, 61 patients were administrated intravenously with LBP 30 mg/m^2 and TXT 75 mg/m^2 on d1; whereas in TXT alone group, 71 patients received TXT at the same dose as in combined regimen group without LBP. Each cycle was repeated every 21 days. The RR and DCR in combined group and TXT alone group were 29.5% (18/61), 67.2% (41/61) and 11.3% (8/71), 45.1 % (32/71), respectively. The median PFS were 4.37 months in combined regimen group and 3.17 months in TXT alone group. There were obvious statistics differences between each other in RR, DCR and PFS. The major toxicities were reversible bone marrow suppression. In combined group, Grade III/IV leukopenia rate and thrombocytopenia rate were 6.8% and 4.1%, respectively, which were significantly higher than those in TXT alone group. He *et al* [13] reported 42 patients with advanced NSCLC were divided into observation group and control group. Observation group (n = 27): LBP 30 mg/m^2 iv, d2; TXT 75 mg/m^2 iv, d1. Control group (n = 27): TXT 75 mg/m^2 iv, d1, repeated 21 to 28 days for the two groups. All the patients could be evaluated. The DCR and response rate of observation group were 73.3% (11/15), 26.7% (4/15), and 63.0% (17/27), 22.2% (6/27) in control group. There was no statistical difference between the two groups. The median survival time in observation group was 18.0 months, which was longer than the median survival time of 14.0 months in control group. The median PFS of observation group and control group were 11.0 months and 7.8 months, respectively. There was no significantly statistical difference in neutropenia, anemia and gastrointestinal reactions between the two groups; the rate of thrombocytopenia was higher in observation group.

Currently, there has been insufficient high-level evidence for the use of LBP as a second-line treatment for NSCLC. However, considering the efficacy of LBP alone or TXT alone as the second-line treatment for NSCLC, further evaluation is required for this combination regimen.

LBP in combined regimes have a substantial efficacy in the treatment for recurrence or metastatic lung cancer, and the major toxicities were reversible bone marrow suppression and gastrointestinal reaction. The types

and severity of toxicities were related to the dose and the drugs of the combination regime.

Breast cancer

Anthracycline-based chemotherapy is widely regarded as one of the first-line treatment of breast cancer. However for the failure of first-line treatment with breast cancer, the second-line treatment drugs include taxane, vinorelbine, gemcitabine and platinum.

Deng *et al* [14] reported 19 cases of metastatic breast cancer who had previously received an anthracycline or a taxane in either adjuvant or metastatic settings. All patients were treated with LBP 35 mg/m^2 d1 and pemetrexed 500 mg/m^2 d1, every 21 days. All eligible 19 patients were evaluable. Overall, 3 (15.8%) patients achieved partial response, 11 (57.9%) SD, 5 (26.3%) progression of disease, with no complete remission. RR was 15.8%, DCR was 42.1%. The major toxicities were bone marrow suppression. The rates of grade III/IV neutropenia and grade III/IV thrombocytopenia were 52.7% and 21.3%. The other study [15] reported these results: 43 patients with advanced breast cancer used the same regimen as used in the study of Deng: no CR patient, 11 cases of PR, 19 cases of SD and 13 cases of PD. The RR was 25. 6%, and the DCR was 69. 8%. The median PFS was 4.2 months. The main side effect was myelosuppression, which was alleviated by symptomatic treatment. The rates of grade III/IV leukopenia and thrombocytopenia were 55.8% and 22.3%, respectively.

Xiao *et al* [16] reported their study as follows: 22 patients with advanced breast cancer accepted LBP plus capecitabine chemotherapy. 16 cases were in second-line or above therapy. No CR patient, 5 cases of PR, 7 cases of SD and 4 cases of PD. The RR was 31.3% and the DCR rate was 75%.

Liu *et al* [17] analyzed the preliminary results of 20 cases of recurrence or metastasis breast cancer using paclitaxel liposom 135 mg/m^2 d1 plus LBP 30 mg/m^2 d2 as the second-line or above treatment: 5 cases of CR patients, 8 cases of PR, 8 cases of SD and 9 cases of PD. The RR was 43.3%. The main side effect was myelosuppression. The rate of grade III/IV leukopenia was 16.6% and the rate grade III thrombocytopenia was 10%.

Zhang *et al* [18] reported 42 cases of advanced breast cancer who had previously received an anthracite nucleus drugs. All patients were treated with TXT 75 mg/m^2 d1 and LBP 35 mg/m^2 d1, repeated every 21 days. Overall, 4 patients achieved CR, 19 patients PR, 11 patients SD, and 8 patients PD. RR was 54.3% and 1-year survival rate was 64.3%. Alopecia, leukopenia and thrombocytopenia occurred in 81%, 19% and 23.8% of patients who had grade III/IV toxicity.

Zhang *et al* [19] reported their results: to investigate the efficacy and toxicity of gemcitabine combined LBP regimen for anthracycline and taxane resistant metastatic breast cancer. Thirty-three patients were treated by gemcitabine 1000 mg/m^2, d1, d8 combined with LBP 30 mg/m^2, d2. The treatments were repeated every 21 days. The RR was 43.7%. The median TTP was 5.8 months. Myelosuppression and gastrointestinal reaction were the most common toxicities. The rates of grade III/IV neutropenia, grade III/IV thrombocytopenia and grade III/IV nausea were 28.2%, 31.3% and 25%, respectively. Treatment related toxicities were tolerable.

Xu *et al* [20] analyzed the results of recurrence or metastasis breast cancer using Vinorelbine at a dose 15 mg/m^2 on day 1 and 8 plus LBP 30 mg/m^2 on day 1 of a 21 days cycle. The RR for first-line treatment was 58.9% and 25% for the second-line or above treatment. There was significantly statistical difference in efficacy between first-line treatment and the second-line or above treatment. The main side effect was myelosuppression. The rates of grade III/IV leukopenia grade III/IV thrombocytopenia and grade III/IV anemia were 42.4%, 9.1% and 9.1%, respectively. Other studies also applied the same regime for anthracycline, taxane, and DDP resistant metastatic breast cancer [21–22]. Overall, these results were encouraging and well tolerated.

Therefore, LBP combined taxanes chemotherapy regimens had substantial efficacy in the treatment of recurrence or metastasis breast cancer. However the effect was more outstanding in the regimen of LBP combined with TXT [18]. Myelosuppression, alopecia and gastrointestinal reaction were the most common toxicities. Considering the main toxicity of LBP was myelosuppression, we thought alopecia and gastrointestinal reaction was related to taxanes.

Gastrointestinal cancer

Lin *et al* [23] reported the results of combination chemotherapy with LBP plus 5-Fu/calclum folinate in the treatment of advanced gastric or colorectal cancer. Thirty-one patients were treated by 5-Fu 300 mg/m^2 or the maximum dose 500 mg/d, d1–d5 combined with calclum folinate 100 mg/m^2, d1–d5 and LBP 30 mg/m^2 d1. The treatments were repeated every 21 days. One patient achieved CR, 8 patients had PR, 16 patients had PD, and the ORR was 22.6% and DCR was 67.8%. The median TTP was 3.0 months. The main toxicity was myelosuppression, with grade III thrombocytopenia in 6.5% patients and grade I/II leukopenia in 35.5% patients. Anemia rate was 41.9%. Liu *et al* [24] studied the effects of LBP or oxaliplatin (OXA) combined with tegafur in the treatment of advanced gastric cancer. Total of 94 cases of advanced gastric cancer were treated with regimen A and regimen B. It included 39 cases of first-line patients and 55 cases of second-line

or above patients. Regimen A: tegafur 800 mg/m^2, continuous intravenous infusion (24h), d1–5; leucovorin 200 mg/m^2, ivgtt (2h), d1–5; oxaliplatin 135 mg/m^2, ivgtt (2h), d1. Regimen B: tegafur 800 mg/m^2, ivgtt, dl–5, leucovorin 200 mg/m^2, ivgtt (2h), dl–5; oxaliplatin 135 mg/m^2, ivgtt (2h), d1. Regimen C: tegafur 800 mg/m^2, continuous intravenous infusion (24 h), d1–5; leucovorin 200 mg/m^2, ivgtt (2h), d1–5, LBP 35 mg/m^2, ivgtt, d1. The regimens were repeated every 28 days. In conclusion,the study of LBP or OXA combined with tegafur in the treatment of advanced gastric cancer was safe and effective. There were 5 CR, 16 PR cases in the regimen A; 4 CR, 16 PR cases in the regimen B; 7 CR, 16 PR cases in the regimen C. The RRs of regimen A, B, C were 65.5%, 66.7% and 71.9%, respectively. The main toxicities were myelosuppression and gastrointestinal reaction. The effect of regimen C was better than that of regimen A and regimen B. However the difference did not reach the level of statistical significance. Tong *et al* [25] reported the results of LBP and OXA in the treatment of recurrence or metastasis colon and rectal cancers. All patients had a history of chemotherapy. Each group had 30 cases. They were treated with LBP 50 mg/m^2, on d1 or OXA 130 mg/m^2, on days 1 combined with calcium levofolinate 200 mg/m^2, d1–d3 and 5-Fu 500 mg/m^2 d1–3. The treatments were repeated every 21 days. Short-term response and survival rate did not reach the level of statistical significance. Myelosuppression rate in the group of LBP was higher than that of OXA group. While neurotoxicity rate in OXA group was higher than that of LBP group.

In conclusion, LBP or OXA combined with calcium levofolinate and 5-Fu had no statistical difference effect in the treatment of recurrence or metastasis gastric or colorectal cancer. The toxicities were mild, but the types of toxicity were different. Myelosuppression rate in LBP group was higher than OXA group; while neurotoxicity rate in OXA group was higher than LBP group.

Ovarian cancer

In the study of Gietema [26] 22 cases of recurrent ovarian cancer patients were treated by LBP 30–50 mg/m^2. 21 patients were assessable for response. 4 patients achieved CR, 1 patient had PR, 2 patients had SD, and 14 had PD. The ORR was 24% and the median OS was 8.0 months. It suggested LBP was effective for recurrent ovarian cancer. However, Kavanagh *et al* [27], reported no objective responses were observed in platinum-resistant epithelial ovarian cancer patients treated by LBP 40–50 mg/m^2.

Lin *et al* [28] reported 22 cases of recurrent ovarian cancer patients who treated with DDP or carboplatibn, received LBP 30 mg/m^2, on days1 and paclitaxel 135–150 mg/m^2, on d1 or TXT 75 mg/m^2, on d1, repeated every 21 days. 2 patients achieved CR, 10 patients had PR, 8 patients had SD, and 2 had PD. The ORR was 45.5%. The main toxicities were myelosuppression and alopecia, with grade III/IV leukopenia in 36.4% patients and grade III/IV alopecia in 9.1% patients.

In Europe, LBP alone was not satisfied with the treatment of ovarian cancer. However, in China LBP in combined regime was often used to treat recurrent ovarian cancer, and the efficacy might be better. The major toxicity was myelosuppression, which could recover after symptomatic treatment. But few researches have been reported in this field and further studies are needed.

Other tumors

Zhai *et al* [29] evaluated LBP combined with recombinant human endostatin injection (endostar) to treat malignant ascite by injection of LBP into the thoracic or abdominal cavity. Thirty-five cases had history of multiple regimen chemotherapy or radiotherapy or intracavitary chemotherapy. 8 patients achieved CR, 16 patients had PR, 8 patients had SD, and 3 had PD. The ORR was 68.57%. Twenty-six cases improved the quality of life and 6 patients had stable quality of life. LBP combined endostar intracavitary chemotherapy in the treatment of malignant pericardial effusion, pleural effusion and ascites was effective, which significantly improved the symptoms of chest tightness, abdominal distension, loss of appetite, dyspnea and quality of life. Stemburg *et al* [30] reported 22 cases of histologically proven bidimensionally measurable metastatic or locally advanced urothelial tract tumors. Two of the 17 (12%) evaluable patients obtained a PR. Of note, neither of these two patients had had prior carboplatin or DDP. Jung *et al* [31] evaluated the combination regimen of LBP, methotrexate and vinblastine in the treatment of transitional cell cancer. One patient had a CR and 2 patients had a PR. The RR was 60%. LBP as the first-line treatment in the treatment of transitional cell carcinoma of the urinary tract played a role, but not in second-line treatment. In China, there were few studies in this area, we need more actively trying. Degarsin *et al* [32] had reported the treatment in head and neck squamous cell carcinoma, but the effects were not clear, and further exploration is needed. Several researches reported LBP-based chemoembolization might be effective for recurrent hepatocellular carcinoma (HCC) patients based on small-sample studies, and LBP-based chemoembolization could improve the OS [33–35]. LBP might be a new choice of the treatment of HCC. However large sample studies are needed to confirm the efficacy.

Due to lack of systemic researches for advanced urinary system cancer and head and neck tumors, we should take an active attempt and application to accumulate clinical experiences.

Toxicity

Clinical data [36] showed that: LBP combined with TXT could cause a high incidence of anemia; while LBP combined with gemcitabine, etoposide, irinotecan or paclitaxel could cause a high incidence of neutropenia. However, most studies were of low statistical efficiency because of small sample size, large range in patients' age and the variation of chemotherapy cycles. Additionally the follow-up time was short, so the long-term effects remained to be unclear.

The main toxicity of the LBP is myelosuppression. Thrombocytopenia is particularly to be noted, which is the main dose-limiting toxicity. Thrombocytopenia usually appears 7–10 days after chemotherapy, 10–14 days to the nadir and 3 weeks recovery. If indicated clinically recombinant human interleukin-11 should be administrated for the patients [4]. The incidence of Grade III/IV thrombocytopenia varied widely, which were from 4.1% to 80% [12–14]. The other common side effect is gastrointestinal reaction, which can recover after symptomatic treatment. But the incidence of gastrointestinal is significantly lower than that of DDP [6].

Summary

In conclusion, LBP was one of third-generation platinum, which has a broad antitumor activity, low toxicity, good tolerance, and no cross-resistance with other platinum drugs [1–3]. LBP in combination chemotherapy showed a substantial effect for advanced patients after first-line chemotherapy. However, the current published literature mostly was in small sample size, single-center study and lack of results from large sample, multi-center, randomized controlled trials.

The recommend dose of LBP alone was 50 mg/m^2 [4, 37] based on the researches from Europe. However, no phase I/II studies of LBP were conducted based on Chinese patients. Given the differences in the physique between Eastern and Western patients, it is unclear whether the results are applicable to Chinese patients. Studies have shown the tolerance of the Oriental was lower than that of the Western [38–39]. Our previous studies also have shown that the eastern and the western had different tolerance to the same dose of chemotherapy. The maximum-tolerated dose of the eastern was equivalent 70%–80% of the maximum-tolerated dose of the western in combination regimes [40–42]. The general recommend dose of LBP is 30–50 mg/m^2, in which 50 mg/m^2 is for mono-drug regimen, 30 mg/m^2 for combination regimes, repeat 21–28 days in China [4]. However in clinical practice a large variation in the application doses, side effects and tolerance were reported [12–13, 43]. Patients who received second-line and above therapies usually have poor physical conditions, and tolerance to chemotherapy might be not as good as for first-line chemotherapy. The chemotherapy dose in combination regimens might be less intense compared with mono-drug regimen. For these reasons, we recommend to conduct phase I/II trials to explore a maximum-tolerated dose of LBP in combination regimen for patients with advanced cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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