

## Irinotecan-Based Chemotherapy for Malignant Pleural Mesothelioma

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### Abstract

*The incidence of malignant mesothelioma (MM) is rising along with the increasing use of asbestos epidemiologically. MM is a highly lethal and particularly refractory tumor. Several phase II and III studies against MM have been performed over the past 2 decades to demonstrate response rates of 0 to 48 %, with median survivals of only 7-15 months. Irinotecan (CPT-11) is a potent topoisomerase I inhibitor and has a definite cytotoxic activity against mesothelioma in the preclinical studies. Intravenous administration of CPT-11 can produce adequate distribution of CPT-11 and the more active metabolite SN-38 into the pleural fluid and allows SN-38 to come into contact with mesothelioma cells in the thoracic cavity. CPT-11 (125mg/m<sup>2</sup>) seems to have minimal single-agent activity in patients with MM, however it has a response rate of 26% (CPT-11: 60mg/m<sup>2</sup>) and 24% (50mg/m<sup>2</sup>) in doublet combinations with cisplatin (CDDP), and 41% (100mg/m<sup>2</sup>) in triplet with CDDP+Mitomycin C. However, high dose CPT-11 (190-200mg/m<sup>2</sup>) has no activity with docetaxel, and 14.2% with gemcitabine. CPT-11 is clearly a useful agent against MM, and is worthy of further study in combination with other drugs. CPT-11-based treatments for the patients with MM will be discussed.*

Malignant pleural mesothelioma (MPM) is an uncommon malignancy that is locally invasive and rapidly fatal. It is usually related to asbestos exposure. Demographic exposure data indicate that its incidence is expected to further increase in the next decade in most industrialized countries. The natural history of MPM is characterized by a median survival of 9-14 months, with < 5% of patients surviving for 5 years. Disease extent at diagnosis and histologic subtype are the main prognostic factors impacting on survival. MPM is refractory to treatment. The majority of patients with mesothelioma are not candidates for curative

surgical resection. Chemotherapy has yielded only modest results in these patients. Antineoplastic drugs, including doxorubicin (DXR), detorubicin, epirubicin, cyclophosphamide, ifosfamide, mitomycin (MMC), methotrexate, edatrexate, carboplatin, and cisplatin (CDDP), have demonstrated some activity against MPM, although their single-agent response rates are disappointingly low. Several combinations of these agents have been tested in many phase II studies, but the role of drug combinations in the treatment of MPM remains unclear. Therefore, there is a critical need for newer and more effective chemotherapy regimens as the incidence of MPM continues to increase internationally.

Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin and a promising new agent. It is a potent inhibitor of topoisomerase I activity and has demonstrated pronounced activity against various experimental tumors, including those that show pleiotropic drug resistance. In phase II trials evaluating single-agent CPT-11 therapy, significant activity has been shown against nonsmall cell lung cancer (NSCLC), achieving response rates of 31.9-34.3%; against small cell lung cancer, achieving a response rate of 47%; and against colorectal cancer, achieving response rates of 20.5-32%. In a preclinical study, CPT-11 also demonstrated cytotoxic activity against mesothelioma using a colony-forming assay.

The activity of single-agent CPT-11 (125 mg/m<sup>2</sup> given weekly for 4 weeks, every 6 weeks) in malignant mesothelioma was investigated by the Cancer and Leukemia Group B (CALGB). In 28 patients evaluable for analysis, no complete or partial responses were observed and the median overall survival was 7.9 months, indicating that CPT-11, at least in this dose and schedule, had no antitumor activity and considerable toxicity (leucopenia, neutropenia, diarrhea) [1].

Furthermore, we evaluated the combination of CPT-11 and CDDP. Fifteen previously untreated patients with MPM were treated with CDDP (60 mg/m<sup>2</sup> on Day 1) and CPT-11 (60 mg/m<sup>2</sup> on Days 1, 8 and 15) administered intravenously and followed by a 1-week rest period. The course of treatment was repeated every 28 days. Ten patients had epithelial subtype, four had biphasic subtype, and one had fibrosarcomatous subtype. Prior asbestos exposure was documented in 4 of 15 patients. One patient had stage II disease, seven had stage III disease, and seven had stage IV disease. Four partial responses (response rate of 26.7%) with a median response duration of 25.9 weeks and two regressions of evaluable disease (overall response rate of 40%) were observed. The median survival time after chemotherapy was 28.3 weeks, and the median time to treatment failure was 22.1 weeks. The 1-year survival rate for all patients was 38.5%. Toxicity was well tolerated, and there were no treatment-related deaths. World Health Organization Grade 3 leukopenia occurred in three patients (20%), and Grade 1 or 2 diarrhea occurred in three patients (20%). The combination of CDDP and

CPT-11 had definite activity against MPM and was well tolerated. The intravenous administration of CPT-11 produced adequate distribution of CPT-11 and its active metabolite SN-18 into the pleural fluid and allowed a higher concentration of the more active SN-38 to make contact with mesothelioma cells in the thoracic cavity [2].

Recently, Le et al (2003) published retrospective data of the same combination in 17 patients with peritoneal mesothelioma. CDDP at a dose of 60 or 50 mg/m<sup>2</sup> was administered intraperitoneally on day 1 if the abdominal cavity was free of adhesions. The same dose of CDDP would be administered intravenously, if a peritoneal catheter could not be inserted. One hour after the completion of the CDDP infusion, CPT-11 60 or 50 mg/m<sup>2</sup> was administered intravenously. The same dose of CPT-11 was repeated on days 8 and 15 of a 28-day cycle. A maximum of six cycles was given every four weeks. Twelve patients (70%) had epithelial mesothelioma, one had mixed sarcomatous and epithelial forms, and four had mesothelioma otherwise not specified. A total 71 cycles of treatment were administered to the 17 patients. Eight of the patients completed the planned six cycles. The median number of cycles per patient was 5 (mean, 4.2). Eight patients received CDDP intraperitoneally for five cycles and intravenously during the sixth cycle. Partial responses were observed in four patients (24%). Of six patients with ascites, two had complete resolution of the ascites, and for the other four, the rate of ascites reaccumulation slowed significantly. The amount of disease remained stable in nine patients (52%). Four patients had progression of disease after two courses (24%). One patient had grade 3 emesis and required hydration and intravenous antiemetic agents several days after intravenous CDDP therapy. Median survival has not been reached [3].

Steele et al conducted a phase II trial of CPT-11, CDDP and mitomycin C (MMC) for patients with untreated MPM. 22 patients with MM were treated with CDDP (40 mg/m<sup>2</sup> on Days 1 and 15), CPT-11 (100 mg/m<sup>2</sup> on Days 1 and 15) and MMC (6 mg/m<sup>2</sup> on Day 1) administered intravenously. The course of treatment was repeated every 28 days. Treatment continued up to six cycles. 15 patients had epithelial subtype, two had biphasic subtype, and five had sarcomatous subtype. One patient had stage I disease, four patients had stage II disease, nine patients had stage III disease and eight had stage IV disease. Nine partial responses and six stable disease of evaluable disease were observed. Four patients were inevaluable for response. Response rate by intent-to-treat was 41%. Grade 3 neutropenia occurred in 61% patients, and Grade 4 neutropenia occurred in 6% patients. Grade 3 diarrhea occurred in 7 % patients [4].

An Italian group (Ferrari et al, 2002) evaluated the combination of CPT-11 and gemcitabine (GEM). 15 patients with malignant mesothelioma were treated with GEM (1000 mg/m<sup>2</sup> on

Days 1 and 8) and CPT-11 (200 mg/m<sup>2</sup> on Day 1) administered intravenously. The course of treatment was repeated every 3 weeks. Five patients had stage II disease, three patients had stage III disease, and three patients had stage IV disease. Two partial responses (14.2 %) were observed. Grade 3 neutropenia occurred in one patient. Grade 4 vomiting occurred in one patient and grade 3 diarrhea in one patient. Grade 4 dermatological toxicity occurred in one patient. There was no treatment-related death [5].

Knuutila et al (2000) evaluated the combination of docetaxel (DOC) and CPT-11. Fifteen previously untreated patients with MPM were given DOC 60 mg/m<sup>2</sup> followed by CPT-11 190 mg/m<sup>2</sup> on day 1, repeated every 3 weeks. Eight patients had epithelial subtype, three had mixed subtype, two had sarcomatous subtype and two had mesothelioma otherwise not specified. Three patients had stage III disease and twelve patients had stage IV disease. No objective responses (complete or partial) were achieved, but three were two minor responses (overall response rate 15 %) each of a duration of four months. Three patients had stable disease (23 %); median time to progression was seven months. Median survival in all the patients was 8.5 months from the first chemotherapy cycle. Toxicity was severe with seven of 15 patients suffering neutropenic fever and six of 15 patients grade 3-4 diarrhea. The trial was discontinued because of toxicity and lack of activity [6].

As mentioned above, CPT-11 has demonstrated activity in the treatment of MPM, but low dose use is recommended.

## References

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