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PROTRACTED INTRAVENOUS INFUSION OF 5-FLUOROURACIL IN COMBINATION TREATMENTS

A review

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Abstract

5-fluorouracil (5-FU) administered by protracted intravenous infusion has been shown to have clinical utility against colorectal cancer and several other advanced tumors. However, additional therapeutic strategies are needed to further improve treatment results. Although the addition of low-dose cisplatin appeared to improve the clinical activity of 5-FU infusion in early phase II studies, subsequent evaluation has failed to substantiate these early reports. In addition, toxicity has been significantly increased. Combinations of cisplatin and other drugs with 5-FU infusion are currently being evaluated. Phase I studies demonstrate that only low doses of concomitant leucovorin are necessary to potentiate 5-FU infusion; phase II studies to evaluate efficacy are underway. Although combinations of 5-FU and biological therapies such as alpha 2a-interferon appear to be very promising, they will require extensive phase II and III testing to define their clinical utility and toxicity.

Key words: Cancer, chemotherapy, 5-fluorouracil, i.v. infusion, combination treatments.

Since the initial phase I report by Lokich et al. (1) demonstrating that 5-FU could be administered by protracted intravenous infusion, numerous phase II and III clinical studies have been completed (2–22). In colorectal cancer the response rate is increased when 5-FU is administered by protracted infusion compared with a bolus schedule (6). Phase II studies have also demonstrated utility in the treatment of breast (13, 16–18, 20–21) prostate (22), gastric (15), and pancreatic cancers (14). Toxicity consists predominantly of stomatitis and hand-foot syndrome with minimal myelosuppression or other major organ toxicities (1, 6, 7). When toxicity is encountered it is easily managed with brief infusion interruption and subsequent dose reduction.

Despite these encouraging results with 5-FU infusion very few complete responses have been observed and most patients become refractory to treatment in 6–9 months (6, 7, 13–15). Because of its favorable toxicity profile, 5-FU infusion could potentially be an ideal drug to combine with other therapies to improve complete response rates and overall treatment results. The purpose of this paper is to review the recent studies (Table) that have combined other drugs with 5-FU infusion to identify which approaches offer the most promise for future trials.

Cisplatin

Preclinical studies have demonstrated synergism when cisplatin (DDP) and 5-FU are utilized together (23, 24). In view of their essentially non-overlapping toxicity profiles, they could represent an ideal combination approach. Cantrell et al. (25) reported preliminary results of a phase II study utilizing 5-FU by protracted infusion and weekly low-dose DDP in patients with metastatic colorectal cancer. Objective response was seen in 20 of 32 patients (63%) with a median duration of response of more than 6 months. Complete remission was observed in 5 patients (16%) which is substantially higher than that which has been obtained with 5-FU infusion alone. Other phase II studies have also evaluated this drug combination (18, 26–30). The Mid-Atlantic Oncology Program (MAOP) performed a phase III randomized study of 5-FU infusion 300 mg/m^2/day with or without weekly DDP 20 mg/m^2

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Table

Agents combined with protracted 5-FU infusion

Ref.	Agent(s)	Phase	Disease	No. of patients	Response %
25	Cisplatin	II	Colorectal	32	63
30	Cisplatin	II	Colorectal	38	37
31	Cisplatin	III	Colorectal	108	35
27	Cisplatin	II	Colorectal	24	42
32	Cisplatin	II	Pancreatic	55	16
34	Cisplatin/ mitomycin-C	II	Colorectal	21	38
35	Doxorubicin/ mitomycin-C/ cisplatin	II	Gastric	10	40
36	Leucovorin/ cisplatin	I/II	Gastric	8	–
38	Methotrexate/ leucovorin	I/II	Colorectal	13	–
39	Leucovorin (i.v.)	I	Colorectal	19	–
40	Leucovorin (p.o.)	I	Colorectal	16	–

(31). Preliminary results with 108 evaluable patients with metastatic colorectal cancer were recently reported, indicating response rates of 31% and 35% for those patients receiving 5-FU or 5-FU and DDP respectively. The difference in the response rates is not statistically significant and there is no difference in survival. The role of weekly low-dose DDP is also being evaluated in an ongoing phase III study in the Eastern Cooperative Oncology Group (ECOG) (Protocol EST 2286).

The role of low-dose DDP potentiation of 5-FU infusion is also being investigated in a MAOP phase II study in metastatic pancreatic cancer (32). Fifty-five patients received 5-FU infusion 300 mg/m^2/day continuously for 70 days followed by a 2-week rest. Weekly cisplatin 20 mg/m^2 was administered weeks 1 through 10. The combination was repeated every 12 weeks until documented disease progression occurred, or unless it was discontinued due to treatment-related toxicity. Two complete and 7 partial responses were seen in 55 patients for an overall response rate of 16%. Average duration of response was 82 days and median survival was 5.8 months. This does not appear to be substantially different for that which has been reported with 5-FU infusion alone, where a 19% response rate and a median survival of 24 weeks were observed (14).

The 5-FU/DDP regimen is significantly more toxic than 5-FU alone. In the MAOP study in pancreatic cancer patients lost an average of more than 3.5 kg of body weight while on treatment with significant fall in performance status in many patients (32). Overall, 24 of the 55 patients (44%) experienced severe treatment-related toxicity at some time in their treatment course and 2 patients had severe life threatening toxicity. In a different study in 18 patients with advanced cancers receiving 5-FU infusion and weekly low-dose DDP excessive toxicity was also encountered (33). Ten of the 18 patients (56%) developed multiple (4 or more) toxicities during treatment. In 10 patients (56%) the toxicity was categorized as severe. Seventeen of these 18 patients (94%) required treatment interruption or dose attenuation due to toxicity and most patients experienced a decline in ECOG performance status due to treatment-related toxicity. Compared with historical toxicity patterns with 5-FU infusion alone (7, 13–15), the addition of DDP resulted in significant increases in nausea and vomiting, anorexia, diarrhea, stomatitis and myelosuppression (33).

In view of the increase in toxicity when weekly low-dose DDP is added, phase III studies must clearly domonstrate improvement in response rates and hopefully survival compared with 5-FU infusion alone, before the combination can be recommended for routine use.

Cisplatin and other drugs

Three other studies utilizing 5-FU infusion, cisplatin and other drugs have been ongoing. In these studies, other active agents with non-overlapping toxicity profiles have been added to further improve results. A phase II study in metastatic colorectal cancer utilizing 5-FU infusion 250–300 mg/m^2/day, DDP 20 mg/m^2/weekly, and mitomycin-C (MTC) 15 mg/m^2/monthly has been recently completed (34). Complete remission was attained in 2 of 21 patients (9%) and partial response in 6 of 21 patients (29%) for an overall objective response rate of 38%. Mean duration of response was 8.7 months (range 6–14) and median survival from initiation of treatment for all patients was 10 months (range 4–29). All patients experienced significant toxicity that required interruption of 5-FU infusion and subsequent dose reduction at some time in their treatment course. Significant thrombocytopenia and leukopenia were observed as well as azotemia, diarrhea and extreme fatigue. In view of the increased toxicity and the lack of apparent improvement in treatment results compared with historical data for 5-FU infusion alone, the 3-drug combination is not recommended (34).

Raschko et al. (35) have reported preliminary results from a phase II study investigating the combination of 5-FU infusion 300 mg/m^2/day, doxorubicin 30 mg/m^2/day 1, mitomycin-C 10 mg/m^2/day 1, and cisplatin 20 mg/m^2/days 8, 22, 36 and 50 (22, 36, 50) in 10 patients with metastatic gastric cancer. The regimen is repeated every 8 weeks. Toxicity has consisted of nausea and vomiting, mucositis, diarrhea, hand-foot syndrome and myelosuppression, but there have been no drug related deaths observed. Objective response has been observed in 4 of 10 patients (40%). It is clear that such combinations will be substantially more toxic than 5-FU infusion alone. Whether response rates and survival are enhanced can only be established with larger trials and longer follow-up.

Leichman et al. (36) have reported the use of neo-adjuvant 5-FU infusion 200 mg/m^2/day plus weekly bolus leucovorin 20 mg/m^2/IV and cisplatin 100 mg/m^2/days 1 and 21 in 8 patients. Five of these patients were able to undergo surgical resection of their primary cancer after chemotherapy administration. Selected patients also received intraperitoneal DDP and FUDR. Thus far, this aggressive approach has been well tolerated without major complications. To date, no information about time to progression, response rates or survival is yet available from this preliminary report.

Leucovorin

Another major method of 5-FU modulation is with calcium leucovorin (CLV). Once intra-cellular 5-FU is incorporated into the substrate fluorodeoxyuridylate monophosphate (FdUMP) which combines in a ternary fashion with thymidylate synthase and 5,10-methylene-tetrahydrofolate. This appears to be the major inhibitory site of 5-FU. This ternary complex has enhanced and prolonged intracellular stability in the presence of extra intracellular folates, which can be achieved by the exogenous administration of CLV. During the last decade there has been considerable interest in the interactions between calcium leucovorin and 5-FU (37). This has been predominantly with 5-FU utilized as a bolus injection. However, a previous phase I/II study suggested the possibility of biochemical interaction between 5-FU infusion and methotrexate/leucovorin (38). Thirteen patients with colorectal cancer were treated with 5-FU by protracted infusion 300 mg/m^2/day, bolus methotrexate (MTX) 200 mg/m^2 every other week and oral leucovorin (CLV) 10 mg/m^2 every 6 h for 4 to 8 doses. This study was abandoned since excessive toxicity was observed in all patients. A significant increase in stomatitis, hand-foot syndrome and diarrhea suggested that potentiation of 5-FU activity did occur. However, it was not clear whether this potentiation was due to MTX, CLV or the combination.

Since then 2 phase I studies have been conducted with 5-FU infusion and CLV. Anderson et al. (39) have reported the results from a phase I study of 5-FU infusion with simultaneous infusion CLV. They concluded that the optimal dose of each drug was 5-FU 200 mg/m^2/day and leucovorin 5 mg/m^2/day respectively. The dose rate limiting toxicity for this combination was stomatitis. Preliminary results of another phase I study utilizing 5-FU infusion and oral CLV have been reported (40). When 5-FU was administered at a dose rate of 200–300 mg/m^2/day with CLV 5 mg orally every 8 h, excessive toxicity was observed. In subsequent patients the dose of 5-FU was decreased to 100 mg/m^2/day and the dose of CLV has been escalated. Sixteen additional patients have now been treated and CLV has been increased to 17.5 mg orally every 8 h. Dose-limiting toxicity has not yet been observed.

Both of these phase I studies demonstrate that very low doses of CLV administered either intravenously or orally, will potentiate the effect of 5-FU infusion. Whereas it has been suggested by some authors that relatively high doses of CLV may be necessary to potentiate bolus 5-FU (37), it is clear that toxicity will preclude the use of relatively high doses of CLV, administered concomitantly with 5-FU infusion. Formal phase II and III studies will be necessary to evaluate the potential clinical utility of such combinations.

Future trials

Future studies will investigate 5-FU infusion in combination with other drugs in diseases where 5-FU has been previously shown to have clinical activity. In addition, methods to further potentiate or modulate the effect of 5-FU infusion will be evaluated; biological therapies are of major interest. Based on preclinical data that suggest that alpha interferon may potentiate 5-FU, Wadler et al. (41) treated patients with colorectal cancer with alpha interferon and 5-FU administered as a 5-day infusion loading course followed by weekly bolus therapy. Objective response was seen in 13 of 17 previously untreated patients. Phase II and III trials will be necessary to further assess the effectiveness and toxicity of similar approaches with protracted 5-FU infusion. In addition, other biological therapies such as Il-2 with or without LAK therapy, tumor vaccines, and monoclonal antibodies may all represent useful methods to further potentiate the effect of 5-FU infusion, in settings where it has already had demonstrated clinical utility.

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