

PROLONGED CYTOSTATIC TUMOR DORMANCY INDUCED BY SERIAL EXCHANGE OF CHEMOTHERAPY IN COLORECTAL CARCINOMA

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ABSTRACT

Background: To improve quality of life cytostatic effect of serially changed chemotherapy was investigated. **Materials and Methods:** Nonrandomized controlled trial in 17 patients with diagnosis of metastasis or recurrence following primary colorectal carcinoma was conducted from 1996 through 2001. Patients underwent low-dose CDDP+5-FU monitoring continual CEA level. Whenever uninterrupted increase for minimally 3 times of CEA level was observed, the next chemotherapy was chosen from the following chemotherapy: *l*-Leucovorin+5-FU, low-dose CPT-11. **RESULTS:** Six were died of carcinoma. Median survival time from primary surgery and those from the day of diagnosis of metastasis were 48.6 and 23.3 months, respectively. Most of the patients experienced decrease in CEA level after continuous increase. No severe side effects were observed in them except one who died of hyperosmolar diabetic syndrome. **CONCLUSIONS:** Although the present trial should await further follow-up to confirm the clinical relevance of its modality, longer survival attained by the serially exchanged chemotherapy would implicate future chemotherapeutic strategy.

Key Words: tumor dormancy, serial exchange, chemotherapy, CEA (carcinoembryonic antigen), colorectal carcinoma

The current flow of cancer chemotherapy has been changed its direction, or true endpoint: from tumor reduction to prolongation of time to progression (TTP). Clinically, anticancer drugs have been estimated by response rate in most carcinoma patients mainly through phase II study, while those drugs have been considered to be less responsible to the solid tumors including gastric, colorectal, or non-small cell lung carcinoma than the others. Moreover, these solid tumors more frequently develop relapse, which leads to poorer prognosis. The correlation between response rates and median survival time (MST) in gastric¹⁾ and non-small cell lung

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carcinoma²) was reported to be negative more likely than not by comparing with more than 20 and 50 contributions, respectively. Conventionally, higher dose of anticancer drugs are expected to be more effective on tumor reduction, the fact is that increasing dose of regimen, or intensive chemotherapy consequently increase drug resistance as well as toxic side effects mediated by suppressing immune system function³) and thereby shortened survival time.

For the improvement of quality of life, prolongation of lifetime would not necessitate tumor reduction, and minimal side effects should be attained by reasonably low-dose chemotherapy especially in time of using strong cytotoxic drugs. Novel strategy of frequent exchanging chemotherapy including low-dose regimen was thence investigated to avoid resistance against cytotoxic agents and induce prolongation of tumor dormant state by continually monitoring carcinoembryonic antigen (CEA) level.

MATERIALS & METHODS

Eligibility of the patients

Those who underwent primary surgery for colorectal carcinoma and were diagnosed as having a relapse during the follow-up period were entered the present trial. Signed informed consent was obtained by all the patients.

Protocol of serially exchanging chemotherapy

Ethical Committee of Nagoya University School of Medicine approved the protocol used in this study.

As the initial treatment of chemotherapy, FP chemotherapy (Fluorouracil-cis-platinum: CDDP+5-FU) was continually administered with the regimen of low-dose CDDP 10mg + 5-FU 500mg/body/one day/week. Low-dose FP, in which CDDP plays a role of biochemical modulator of 5-FU, was initially developed and has been prevailed in Japan of late⁴). The timing of changing chemotherapy was essentially decided according to observation of more than 3 consecutive increase of weekly CEA values.

The subsequent chemotherapy was chosen among the following 2 regimens plus that of initial chemotherapy: LV+5-FU (*I*-Leucovorin 300mg/body/day/week+5-FU 750mg/body/day/week for consecutively 6 weeks of 7 weeks), which has been established as a conventional chemotherapy for more than 40 years⁵); low-dose CPT-11 (40mg/body/week or twice a week). CPT-11 is reported to be effective on 5-FU resistant colorectal carcinoma⁶), also statistically significant in one-year survival time and median survival time as compared with 5-FU/LV in phase III study⁷). The intervals of all the regimens were individually dependent on frequent monitoring of CEA levels. The protocol was discontinued for the meanwhile when severe side effect occurred.

Serum CEA assay

The serum CEA content was measured by enzyme immunoassay (EIA), using Olydas-120 (Olympus Optical Co., Tokyo, Japan), Glaozyme New CEA kit (Wako Pure Chemical Industries, Osaka, Japan). CEA values <5 ng/ml were assessed as normal.

RESULTS

Of 17 patients enrolled the new modality, 7 patients were died of metastatic tumor except one whose death was caused by hyperosmolar diabetic syndrome. No one occurred severe side

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effects, whereas diarrhea, dehydration, and leukopenia (grade 1-2) were observed in 6, 5, and 7 patients, respectively. The leukopenia was normalized in all the patients after administering granulocyte colony-stimulating factor by subcutaneous injection. Reductive effect on CEA value was observed in 16/17 (94%) when chemotherapy was changed. Most of the patients received postoperative chemotherapy at outpatient clinic.

The median and minimal-maximum survival time from primary operation were 48.6, 9.3–99.3 months, respectively (Fig. 1), while those from diagnosis of metastasis/recurrence were 23.3, 9.3–66.6 months, respectively (Fig. 2).

Case history of the new modality (Fig. 3)

A 66-year-old man (case no. 3 in Fig. 1, 2) had an anterior resection with total cystectomy for a sigmoid colon carcinoma with bladder infiltration (T4N2M0) in April, 1999. His postoperative CEA values were satisfactorily stable at a range between 0.7 and 3.6 ng/ml until p.o. 13.6 months. He started to receive chemotherapy with FP (CDDP/5-FU) for once a week at p.o. 15.2 months. After 14 times of administration, as the CEA values showed gradual elevation from 4.7 to 10.1 ng/ml, the decision was made to change chemotherapy to LV/5-FU as the described regimen until p.o. 23.3 months when the CEA values continuously increased from 2.1 to 8.5. Therefore, he started to receive FP again for once a week. After 6 times of completion, CEA values increased from 9.2 up to 10.7, FP chemotherapy was alternated with LV/5-FU again. He developed grade 2 diarrhea, two times of cessation was followed by restart of the same regimen. Two continual increases (CEA values ranged 5.3-38.7 ng/ml) urged him to receive another chemotherapy, FP was administered once a week from p.o. 28.6 months. Subsequent elevation of CEA figure (37.1-103.2) was followed by alternated chemotherapy with CPT-11 at p.o. 30.9 months.

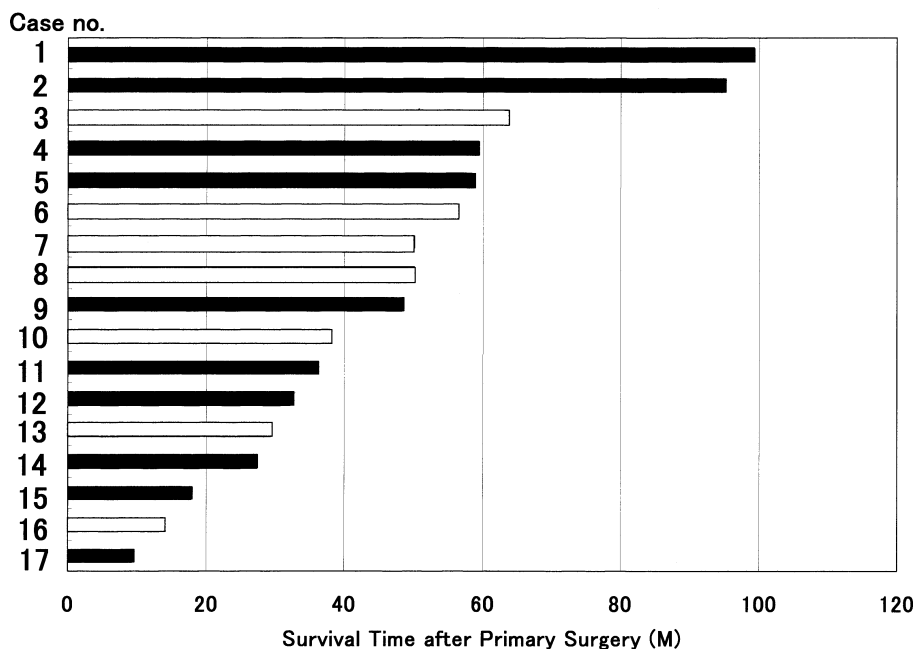


Fig. 1 The survival time from primary operation. The median and minimal-maximum survival time were 48.6, 9.3–99.3 months, respectively. ■: arrival; □: dead cases due to carcinoma.

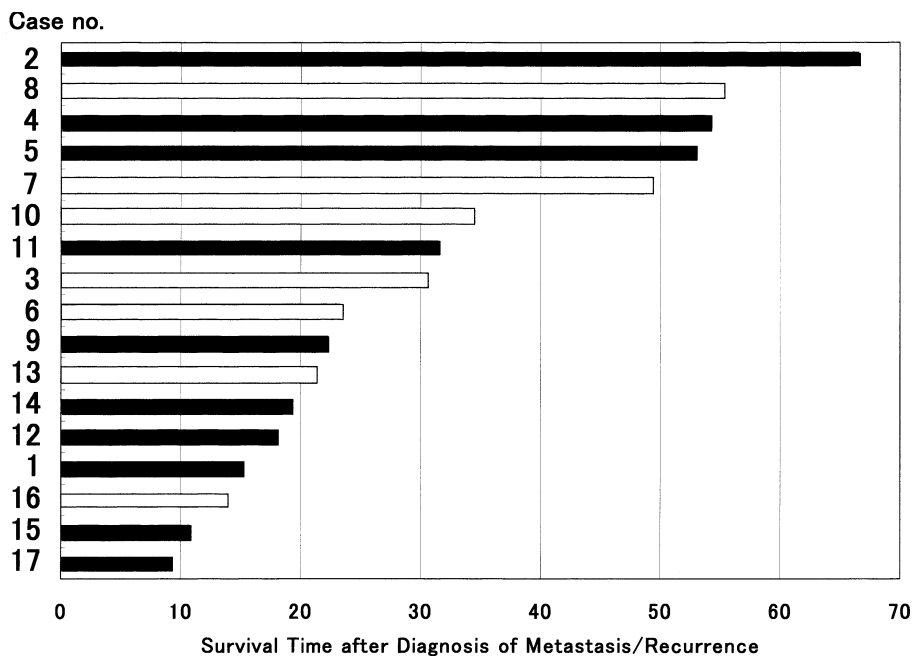


Fig. 2 The survival time from diagnosis of metastasis/recurrence. The median and minimal-maximum survival time were 23.3, 9.3-66.6 months, respectively. ■: arrival; □: dead cases due to carcinoma.

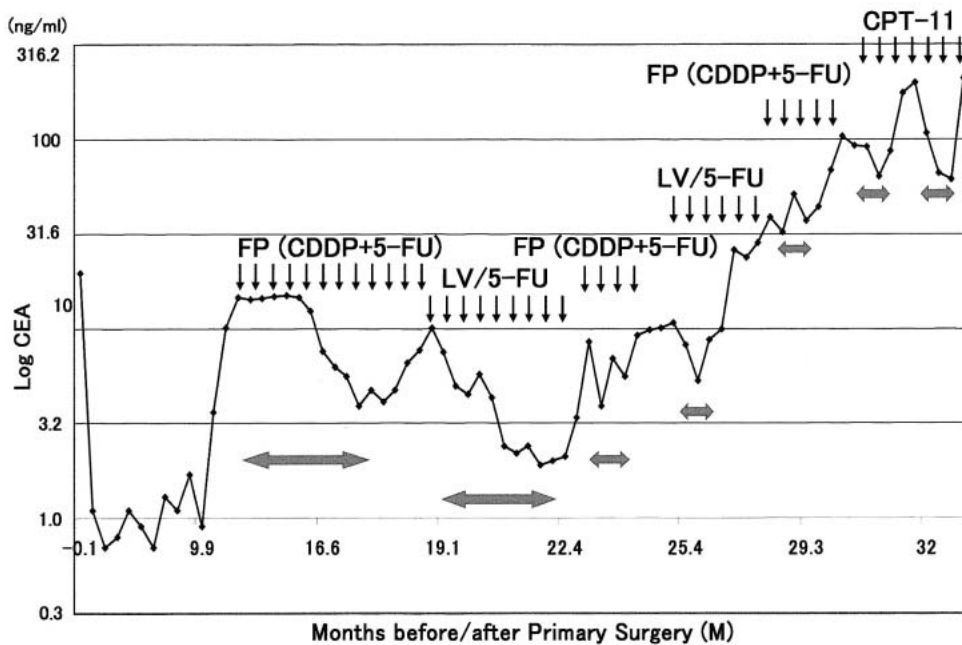


Fig. 3 Serial measurements of CEA through frequent change of chemotherapy: Case no. 3. Duration marked as \longleftrightarrow is associated to be tumor dormant state observed at the time of the change of chemotherapy.

DISCUSSION

The role of chemotherapy has been acknowledged to be not only tumor reduction but also prolongation of survival time without significant response rate. There appears to be no relation between response rate and MST (median survival time), whereas TTP (time to progression) and MST are considered to have correlation. In phase II studies for gastric carcinoma, Takahashi *et al.* investigated the significant difference between 5'-DFUR responder and stable disease (SD) of more than 90 days to progression, concluded that the two groups (CR+PR vs SD) were almost the same in survival curves⁸⁾, also found the similar result in the two groups of CPT-11 responder and SD of more than 90 days⁹⁾.

The transition model of size of solid tumor with the relation of survival time shows that positive chemotherapeutic response (tumor reduction) period would less contribute to prolongation of survival time when compared with length of the cytostatic phase³⁾. Takahashi *et al.*³⁾ thus hypothesized that the prolonged cytostatic phase induced by chemotherapy could also trigger prolongation of survival time without satisfying tumor response^{3,10)}, when the tumor is in the prolonged dormant state for the reason that the size of tumor seems to be almost the same, neither reducing nor progressing. Tumor dormancy is described to be in the state that tumor cells are in mitotic arrest or that the rate of tumor proliferation and cell death are balanced^{11,12)}.

The chemotherapeutic strategy making effective use of the mitotically arrested tumor cells i.e. nonactive dormant cells has not been developed thus far, whilst the novel direction targeted to active tumor cells balancing with apoptotic tumor cells has been advanced with a various approach toward effective prolongation of tumor dormancy state. TNP-470 is one of the expected to be effective fumagillin derivative to prolong tumor dormancy state by inhibiting vascular endothelial cells, using with or without anti-carcinoma drugs¹³⁻¹⁵⁾. Molecular therapy using another anti-angiogenetic agents such as herceptin (anti p 185 HER 2/neu monoclonal antibody)¹⁶⁾ or C225 (anti-EGFr chimerized antibody)¹⁷⁾ has been investigated and found effective results. DFMO (α -difluoromethylornithine), the polyamine inhibitor, has reported to be effective in colorectal carcinoma¹⁸⁾ inducing both antiangiogenesis and apoptosis¹⁹⁾.

To avoid rebounding of cytostatic phase of tumor must also play an important role of prolongation of survival time. The rebound phase is partly ascribed to the resistance against chemotherapeutic agents, decrease of host immunity. A various therapy is thence investigated for gaining benefits by retarding recurrence. Low dose administration of chemotherapy such as CPT-11²⁰⁾, or combination therapy (low-dose CPT-11 plus oral HCFU²¹⁾ or low-dose CPT-11 plus low-dose FP²²⁾ is considered to be effective in preventing from acquiring a tolerance, resulting in prolongation of TTP. Immunochemotherapy intended to protect host immune system against damage induced by anti-tumor drugs is also promising therapy for long-term survival²³⁾.

Here we observed the decrease of CEA value and prolongation of survival time induced by repeated change of the agents. Regarding the acquisition of drug resistance, the protein function of efflux pump to extrude cytotoxic drugs from tumor cells has expected to be involved in this mechanisms. Taking our results into consideration, the function of efflux pump might be transient response, since reuse of the same drug once confirmed resistance, after another course of chemotherapy, seemed to release from the same resistance. In the light of tumor dormant phase, the apoptosis of active tumor cells respondent to one cytotoxic agent might balance in number to the proliferation of those active and/or inactive dormant cells which would not respond to the same agent but another one.

Comparing with the newly results of chemotherapy in Europe and US recently standardized, treatment with CPT-11/5-FU/LV (irinotecan plus fluorouracil, leucovorin) was reported to result in 17.4²⁴⁾ and 14.8 months²⁵⁾ of MST, respectively, which seemed that median MST obtained

(48.6 and 23.3 months, Fig. 1, 2) would show some effect due to serial exchange of chemotherapy.

For the positive estimation of tumor dormant state, matrix metalloproteinase inhibitor, marimastat is used to investigate the antiangiogenic effect categorized into 3 grades: biological effect (BE, decrease in tumor marker from preadministration), partial biological effect (PBE, increase $\leq 25\%$), non-responder (NR, increase $>25\%$). A contribution showed BE+PBE group is significantly longer in over all survival time than that of NR, moreover, BE and PBE was almost the same in survival time²⁶. Although antiangiogenic drugs hardly allow tumor cells to acquire drug resistance, that kind of method for estimation of response should be added to chemotherapy to assess the effect of prolonging tumor dormant phase. Moreover, complex evaluation of CT or MRI in addition to tumor marker such as CEA is to be required to see the sensitivity of the drugs, since liver metastasis of colorectal carcinoma is sometimes less productive of CEA. For the benefit of prolonging tumor dormant state in colorectal carcinoma patients, multiple chemotherapy including cytotoxic agents, molecular targeted agents such as antiangiogenic ones, with a combination of immunotherapy and radiotherapy chosen depending on an individual condition should be investigated in the future in a manner of made-to-order modification, which would be a promising clue for prolonging survival time benefit for active tumor cells in balanced dormancy phase with never reducing QOL. Recently genetic information is clinically used to individualize dosage of chemotherapy with the aim of avoiding as much risk as from cytotoxic agents by precisely knowing individual chemosensitivity beforehand. However, such investigation would be limited according to the affiliations, we thus consider that individually modified, i.e., serially changed chemotherapy based on CEA monitoring would be highly beneficial in terms of both cost and convenience. The mechanism of inactive tumor cells in dormant phase is still unknown, should also be revealed for establishment of a new strategy.

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