Need for a new treatment strategy: leptomeningeal carcinomatosis from gastric cancer

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Leptomeningeal carcinomatosis (LMC) is an extremely rare manifestation of gastric cancer. The treatment options are very limited for LMC; despite standard treatment with intrathecal chemotherapy, the prognosis is grim and the median overall survival is 3–4 months. Here we report on a patient with LMC from metastatic gastric cancer who was treated with a novel approach of high-dose systemic irinotecan, comparable with the dose utilized in treating primary brain tumors such as gliomas. Our patient not only had an excellent tumor response to this novel approach, but also had a prolonged overall survival of 13 months, which is unusual for LMC from gastric cancer. *Anti-Cancer Drugs* 20:301–304 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Leptomeningeal carcinomatosis (LMC) is a devastating neurologic complication of malignancy. LMC is not uncommon in solid tumors including breast, lung, melanoma, and hematologic malignancies such as lymphoma and acute lymphoblastic leukemia [1,2]. However, LMC is a rare manifestation of gastric cancer and has been reported infrequently in the United States [3,4]. Its true incidence is hard to determine given the rarity of the disease. It is more commonly seen in Japan and Korea given the increased incidence of gastric cancer compared to Western countries [5,6].

Here we report on a patient from our institution with gastric cancer who later developed LMC during the past year and was treated with high-dose systemic irinotecan, resulting in complete tumor response. This raises questions about the management strategy most commonly used in the last several decades, that is, intrathecal methotrexate.

Case

The patient is a 62-year-old Korean female who was diagnosed with signet ring gastric cancer, when she presented with reflux symptoms and epigastric discomfort in July 2007. Her medical history was significant for left-sided stage-I breast cancer, diagnosed in 2001 for which she underwent lumpectomy followed by adjuvant radiation and then 5 years of adjuvant hormone treatment with tamoxifen ending in 2006. Subsequent to her diagnosis of gastric cancer, she underwent gastrectomy in August 2007, and was found to have stage IIIA (T3 N1 M0) tumor extending into the subserosa, two out of eight lymph nodes revealing extranodal tumor extension, with focally positive distal margins and lymphovascular invasion.

The patient was referred to oncology for further adjuvant treatment. However, within a few weeks after surgery, she developed severe headache and photophobia, and on physical exam she was noted to have an enlarged left supraclavicular mass (Virchow's node). In September 2007, she underwent fine-needle aspiration of the left supraclavicular mass, which showed metastatic adenocarcinoma consistent with gastric primary by immunohistochemistry staining. MRI of the brain with gadolinium confirmed meningeal enhancement consistent with LMC (Fig. 1a and b). The patient also underwent cerebrospinal fluid cytology, which was consistent with metastatic gastric adenocarcinoma.

The patient suddenly developed aphasia and right-sided weakness before starting systemic chemotherapy. Repeat MRI of the brain showed an acute ischemic stroke involving the left hemisphere. Her treatment was initially delayed for a few weeks because of the ischemic stroke. She was then treated with weekly irinotecan at 125 mg/m^2 [7–9]. Along with irinotecan, she also received 5-fluorouracil 200 mg/m^2, continuous intravenous infusion for 3 weeks, which was later discontinued because of cytopenia and poor tolerance. A repeat imaging work up with brain MRI showed decreased meningeal enahancement after 6 weeks of chemotherapy with improvement in her systemic disease as well. She was continued on weekly irinotecan at the same dose. Meanwhile, in April 2008 she suffered another ischemic stroke involving the same

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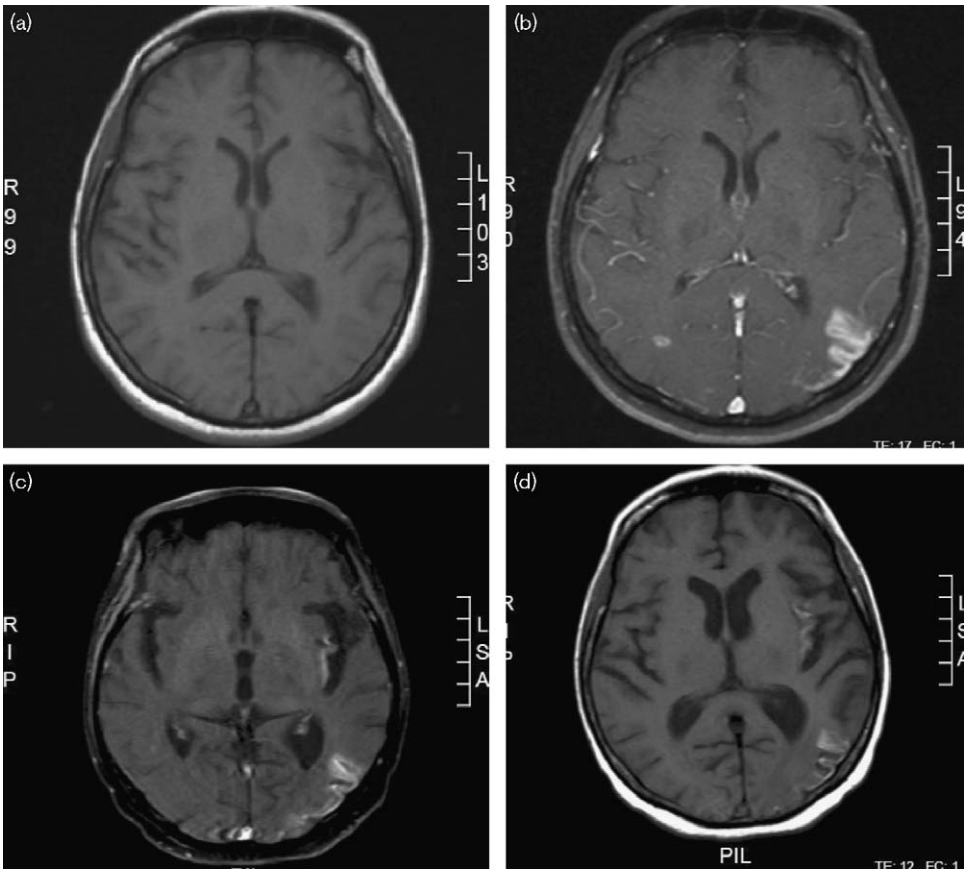
Fig. 1



Serial magnetic resonance imaging of the brain. Before irinotecan treatment: (a) noncontrast MRI shows normal parenchyma with no enhancement. (b) Gadolinium-enhanced MRI shows leptomeningeal enhancement involving the left and right occipitoparietal lobes suggestive of leptomeningeal carcinomatosis. Additional leptomeningeal enhancement is seen in the subcortical frontal and cerebellar hemispheres. Post-irinotecan treatment: (c) noncontrast MRI shows laminar necrosis/encephalomalacia. (d) Gadolinium-enhanced MRI shows no enhancement suggestive of leptomeningeal carcionamatosis, but shows laminar necrosis suggestive of old infarct or scar tissue from prior treatment of leptomeningeal carcinomatosis.

distribution. A repeat MRI at that time showed ischemic stroke involving the left hemisphere, but continued improvement of meningeal enahancement suggestive of a good response to irinotecan. Although her LMC was improving she remained aphasic with residual right-sided weakness from her cerebrovascular disease. Weekly irinotecan therapy was continued until the end of May 2008 for a total of 8 months without major toxicity or need for dose reduction. The patient was allowed to take a break from chemotherapy because of fatigue on a few occasions and during times of acute stroke. A repeat MRI at the end of the chemotherapy in June 2008 suggested a complete response with absent meningeal enhancement (Fig. 1c and d). However, in July 2008 she developed another massive stroke involving the left hemisphere resulting in severe disability. Despite improvement in systemic disease and LMC, the patient suffered recurrent strokes. She was given antiplatelet therapy with aspirin. Except for her cancer, she did not have any risk factors to develop thrombosis. There was no evidence of endocarditis by echocardiogram or other hypercoagulable states. Carotid ultrasound failed to show any other source for her strokes.

Given her disabling neurologic status and deteriorating functional status, a decision was made to stop aggressive intervention. The patient and her family opted for hospice care. She lived until October 2008, for more than a year from her diagnosis of LMC, which is very unusual for LMC from metastatic gastric cancer.

Discussion

Oncologists are faced with challenges involving treatment of LMC, more so in recent years owing to improvement in systemic control of disease with better chemotherapeutic and targeted agents. Treatment options are very limited in LMC. Options include intrathecal chemotherapy, whole-brain radiation therapy, systemic chemotherapy, and best supportive care [10]. Radiotherapy is preferable in patients

Table 1 Clinical trials on treatment of leptomeningeal carcinomatosis

Reference	Study design	Median survival	Toxicity
[17]	$n=52$ IT MTX versus thiotepa	IT MTX = 15.9 weeks IT thiotepa = 14.1 weeks	IT MTX = IT thiotepa
[19][a]	$n=110$ IT Depocyt	IT Depocyt = 95 days	IT Depocyt-arachnoiditis headache
[15]	$n=61$ IT Depocyt versus IT MTX	IT depocyt = 105 days IT MTX = 95 days	IT MTX = IT depocyt
[18]	$n=44$ IT MTX versus IT MTX + ara-C	IT MTX = 12 weeks IT MTX + ara-C = 7 weeks	IT MTX + ara-C > IT MTX
[20][b]	$n=23$ MTX + ara-C + thiotepa		Severe toxicity
[21]	$n=55$ IT MTX versus IT MTX + ara-C	IT MTX- 10.4 weeks IT MTX + ara-C = 18.6 weeks	IT MTX = MTX + ara-C

Depocyt, sustained release ara-C 50 mg every 2 weeks; IT ara-C, intrathecal ara-C 50 mg twice a week; IT thiotepa, intrathecal thiotepa 10 mg twice a week; IT MTX, intrathecal methotrexate 12 mg twice a week.
[a]Compared with historic control-intrathecal methotrexate: median overall survival – 110 days.
[b]No control arm.

presenting with severe neurologic dysfunction, mass lesions with a high tumor burden and poor performance status (Eastern Cooperative Oncology Group performance score of 3 or more); best supportive care is also an option in such patients, especially if they have a poor performance status [2,10–12].

Historically, intrathecal chemotherapy has been the mainstay of treatment. Three drugs that are used include methotrexate, cytarabine, and thiotepa in combination with hydrocortisone. The most common drug in use is methotrexate. Although cytarabine is not an active drug in solid tumors and it is mainly used in hematologic malignancies, it is one of the first-line agents used in the treatment of LMC. From several small case studies and randomized controlled trials, the median overall survival for LMC with either methotrexate or cytarabine remains at 3–4 months. Furthermore, it is apparent that no regimen has a clear and consistent superiority to another [13–20] (Table 1).

Despite some evidence that combination intrathecal chemotherapy is beneficial, it is still controversial whether the use of combination intrathecal chemotherapy in LMC is superior to single agent intrathecal drug administration. A recent comparative study by Kim *et al.* [21] of 55 patients with LMC from solid tumors showed that the combination of intrathecal methotrexate and cytarabine had a superior median survival of 18.6 weeks compared with 10.4 weeks for methotrexate alone . In contrast, an earlier clinical trial by Hitchins *et al.* [18] comprising 44 patients with LMC from solid tumors showed a statistically significant median overall survival for methotrexate alone (12 weeks) compared with combination methotrexate and cytarabine (7 weeks). Combination chemotherapy was associated with more toxicity .

Therefore, there are no definitive guidelines for the management of LMC. Several promising experimental treatments for LMC are in the horizon. There are phase-II studies showing moderate response rates with intrathecal topotecan (22%), intrathecal etoposide (26%), and phase-I studies with intrathecal mafosfamide in solid tumor-related LMC [22–26]. Chemical meningitis is a significant and concerning side effect of intrathecal chemotherapy in the above studies.

Conclusion

Irinotecan, a first-line treatment for metastatic colorectal cancer and an agent with high activity against solid tumors of the gastrointestinal tract, is an inhibitor of topoisomerase I, a critical enzyme needed for DNA transcription [27]. Topoisomerase I inhibitors such as topotecan and irinotecan represent a class of chemotherapy drugs that have been used in primary malignant brain tumors. Among that class, irinotecan readily crosses the blood–brain barrier and has been extensively studied in recurrent glioma [7–9,28]. Recent clinical trials have shown major antitumor activity in recurrent glioblastoma while adding the antiangiogenesis drug bevacizumab with irinotecan at the dose used in our patient (125 mg/m^2 every week) [7–9,29]. The combination of targeted agents to topoisomerase I inhibitors represents a novel and promising approach in recurrent gliomas. Our patient had an excellent response to cytotoxic therapy with weekly irinotecan infusion at a dose of 125 mg/m^2. Although this is a single patient response, as irinotecan is generally an active drug in gastric cancers with its penetrating effect across the blood–brain barrier, it may have utility in treating LMC from gastric cancers and perhaps other solid tumors such as breast and lung cancers. This is the first case report of LMC from metastatic gastric cancer that responded to systemic irinotecan. This therapeutic approach warrants further investigation which is best conducted in the setting of clinical trials.

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