Comparison of Intrathecal Chemotherapy for Leptomeningeal Carcinomatosis of a Solid Tumor: Methotrexate Alone Versus Methotrexate in Combination with Cytosine Arabinoside and Hydrocortisone

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Objective: To compare the efficacy of intrathecal methotrexate single therapy with three-drug combination therapy in patients with leptomeningeal carcinomatosis.

Methods: Fifty-five patients who had pathologically proven leptomeningeal carcinomatosis of a solid tumor were evaluated in terms of pathological response. Group M (n = 29) received methotrexate 15 mg and group MHA (n = 26) received methotrexate 15 mg, hydrocortisone 15 mg/m² and ara-C 30 mg/m² twice a week intrathecally until a cytological response was obtained.

Results: Primary sites of the tumor were the lung (n = 33), breast (n = 13) and stomach (n = 5). The pathology of 45 patients was adenocarcinoma. The cytological response rate to intrathecal chemotherapy was significantly higher in the MHA group than in the M group (38.5 vs 13.8%, P = 0.036). The median survival was 18.6 weeks in the MHA arm and 10.4 weeks in the M arm (P = 0.029).

Conclusion: Combination intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone showed more favorable effects than methotrexate single therapy for leptomeningeal carcinomatosis in solid tumors.

Key words: meningeal neoplasms – spinal injections – methotrexate – cytarabine

INTRODUCTION

Leptomeningeal carcinomatosis (LMC) from solid tumors is a clinically important neurological complication of systemic cancer (1), the presence of which usually indicates a grave prognosis of 4–6 month median survival irrespective of intensive treatments. Since the first case was described in 1870 by Eberth (2), much improvement in the systemic chemotherapy of neoplastic diseases has resulted in an increased incidence of LMC in many types of solid tumors (3).

A diagnosis of LMC can be made with positive cytology in the cerebrospinal fluid (CSF) or by typical findings on neuroimaging studies or by clinical criteria alone, in a patient with known cancer and neurological dysfunctions at multiple levels of the neuraxis (1). As to the treatment of LMC, it is generally accepted that the standard therapy involves introducing chemotherapeutic agents directly into the CSF (i.e. intrathecal or intraventricular chemotherapy) in combination with radiotherapy directed to the areas of major clinical involvement (3). Although there is some debate about the efficacy from the perspective of survival benefit (3,4), many reports have agreed upon the beneficial role of intrathecal chemotherapy on the survival of patients with LMC.

Methotrexate remains the most frequently used drug for intrathecal administration, despite limited success and serious toxicities (5). Other drugs used are cytosine arabinoside (ara-C), thiotepa and L-asparaginase, which have been tried in humans, and the use of which in solid tumor LMC has been extrapolated from data on the treatment of leukemic meningitis (6). The efficacy of single-regimen intrathecal chemotherapy with methotrexate for solid tumor LMC is believed to be un-
satisfactory (1) and many efforts have been made to improve the response rate and survival by combining methotrexate with other agents, such as ara-C and thiotepa.

Several reports have described the use of these drugs in sequence or in combination with methotrexate and many failed to find any superiority of combination therapy over single therapy (3,4,7,8). However, our experience of systemic chemotherapy suggests that chemotherapy based on a combination regimen produces improved treatment results. Also our clinical experience was different from those which others had previously reported about the efficacy of combination intrathecal chemotherapy. We hypothesized that the difference was caused by the different patient populations and the different methods of efficacy evaluation. Therefore, this study was performed to compare retrospectively the efficacies of intrathecal methotrexate single therapy (M) with a three-drug combination therapy (methotrexate, hydrocortisone and ara-C; MHA), using response criteria based on pathological conversion in patients with solid tumors LMC.

PATIENTS AND METHODS

PATIENT ELIGIBILITY

Fifty-five patients with pathologically proven solid tumor LMC (with a positive cytology in the CSF) which was diagnosed consecutively in our center between January 1995 and July 2002 were enrolled in this study. All patients had histologically confirmed malignancy and were not excluded because of the performance status, tumor types or the stage of systemic disease. Patients with acute or chronic leukemia or lymphoid malignancy were excluded.

TREATMENT SCHEME

All patients underwent intrathecal chemotherapy after confirmation of a positive CSF cytology. All chemotherapeutic agents were diluted in sterile normal saline and administered intrathecally by repeated lumbar puncture. No patients underwent Ommaya reservoir placement. The treatment regimen was determined for each patient at the discretion of the attending physician and they followed a common assignment algorithm. A group of patients (n = 29) received methotrexate 15 mg (M) and the others (n = 26) received methotrexate 15 mg, hydrocortisone 15 mg/m² and ara-C 30 mg/m² (MHA) concurrently. Treatment sessions were repeated twice a week and patients were assessed for response by complete clearing of all malignant cells from lumbar CSF. The responders, whose CSF showed no malignant cells or no atypical cells, received a weekly maintenance therapy with the same regimen as the previous one while response persisted. If progression occurred on the M arm, ara-C and hydrocortisone were added. Patients were taken off intrathecal chemotherapy if progression appeared on the combined MHA arm or performance status worsened.

Folic acid was administered at the initiation of the therapy or after the development of myelosuppression at the discretion of the attending physician. Cranial and/or spinal irradiation therapy (RT) was directed towards the symptomatic sites in the neuraxis and towards all bulky disease evident on neuroimaging studies. RT was not assigned randomly; the decision to use RT was made principally if symptomatic areas or mass lesions were present on neuroimaging studies.

CRITERIA FOR ASSESSMENT OF EFFICACY AND ADVERSE EFFECTS

CSF was obtained and examined at each cycle. Serial examinations, including cytology, complete cell count, differential count, glucose and protein, were performed. Neurological status was assessed at the initiation of therapy and was reassessed before each course. Assessment of neurological status was based on the patient’s subjective evaluation of neurological status improvement and the opinion of observer physicians who were not the attending physician. A neurological improvement was defined as a decrease in intensity or a disappearance of the initial neurological symptoms and signs and a neurological response was defined as the presence of neurological stabilization or improvement persisting for at least 4 weeks. Criteria for a cytological response included the complete clearing of

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*Craniand/or spinal radiation therapy. †Systemic chemotherapy.
all malignant cells from lumbar CSF in at least two serial examinations and the presence and continuation of neurological response. To evaluate adverse effects, complete blood cell count and biochemical profiles were monitored at least weekly, if the patient’s performance status permitted.

STATISTICAL METHODS

Comparisons of categorical variables between the two groups with respect to the response data were made using the chi-square test and Fisher’s exact test. Survival curves were generated by the Kaplan–Meier method. Comparisons were deemed statistically significant when the two-tailed $P$ value was $<0.05$.

RESULTS

Twenty-nine patients received M and 26 patients received MHA. The characteristics of all patients and of the patient groups are listed in Table 1. The primary tumors of 55 patients were of the lung (60.0%), breast (23.6%) and stomach (9.1%). Of the other patients, two had rhabdomyosarcoma, and in the two remaining patients the primary site could not be identified.

The median number of cycles of intrathecal chemotherapy in the 55 patients was seven (range: 2–24) – eight in the MHA arm and six in the M arm. The median number of treatments to cytological response in cytological responders was 3.5 (range: 1–9) and there was no statistically significant difference between the two arms (M vs MHA: 4.5 vs 3.5, $P = 0.713$). Cytological response was observed in 14 patients (25.5% of all patients) and neurological response in 36 patients (65.5%). The cytological response rate of the MHA arm was higher than that of the M arm and this was statistically significant (38.5 vs 13.8%, $P = 0.036$). Even though the five patients with small cell lung carcinoma were excluded in the analysis, the response rate of the MHA arm exceeded that of the M arm (27.3 vs 14.3%, $P = 0.302$), but the difference was not statistically significant. The neurological response rate was not different significantly between the two treatment arms (M vs MHA: 58.6 vs 73.1%, $P = 0.260$).

When patients were categorized in terms of primary tumor and histology, patients with small cell lung cancer fared best (4/5 patients, 80.0%), followed by breast cancer (5/13 patients, 38.5%), stomach cancer (1/5 patients, 20.0%) and adenocarcinoma of lung (4/25 patients, 16.0%) in the cytological response rate.

Cytological response rate among patients who did not receive concurrent CNS irradiation was 32.1%, which was higher than those that received CNS irradiation (18.5%), but the difference was not significant ($P = 0.246$). In patients who did not receive CNS irradiation, the difference between the two treatment arms (M and MHA) became more prominent and statistically significant (12.5 vs 58.3%, $P = 0.017$) than for those who received CNS irradiation (15.4 vs 21.4%, $P = 0.686$). The presence of brain and/or spinal parenchymal metastasis did not affect the response rate significantly (31.4 vs 15.0%, $P = 0.178$).

In terms of the neurological response rate, differences in the primary tumor site and the presence of brain and/or spinal parenchymal metastasis did not cause a significant difference, except that the neurological response rate was higher (81.5%) among patients who received concurrent cranial and/or spinal radiation therapy than in those (50.0%) who did not ($P = 0.014$). The duration of neurological response was 5.1 weeks in patients who responded neurologically. We could not obtain the result for the cytological response duration, because for many patients who showed cytological responses further follow-up CSF examinations were not performed to evaluate the cytological response duration, mainly owing to loss to follow-up.

The treatment-related toxicity was tolerable in both treatment arms. No hematological and non-hematological toxicities over grade 3 (WHO criteria) were observed. In the M arm, two patients experienced an episode of grade 1–2 leukopenia and one patient grade 1 neurotoxicity. In the MHA arm, three
patients experienced grade 1–2 leukopenia and one case of elevated hepatic enzyme was reported (grade 1).

Fig. 1 shows the Kaplan–Meyer survival curves of the two treatment arms. The median survival of all 55 patients was 11.9 weeks (range: 2.7–28.7 weeks) and median survival was longer in the MHA arm than in the M arm (18.6 vs 10.4 weeks, \( P = 0.029 \)). Survival was longer in the cytological responders than in the non-responders (22.1 vs 11.6 weeks), but this was not statistically significant (Fig. 2). In terms of the subgroups classified by histology and primary tumor type, patients with adenocarcinoma of the lung in the MHA arm showed a survival advantage over those in the M arm, which was statistically significant (23.9 vs 10.4 weeks, \( P = 0.038 \)). In breast cancer patients, the survival predominance of the MHA arm over the M arm was marked, although it was not statistically significant (23.7 vs 10.1 weeks, \( P = 0.445 \)). Patients with concurrent RT showed an 8-week survival predominance over patients with no RT, although it was not significant statistically (18.6 vs 10.9 weeks, \( P = 0.470 \)).

Among 41 patients who expired and whose causes of deaths were identifiable, 38 patients (93%) died of the progression of CNS lesion. The proportions of patients between the two arms were not different (M vs MHA: 92 vs 94%).

**DISCUSSION**

The treatment results for LMC in solid tumors have not been satisfactory with the current treatment modalities. Many efforts have been made to increase the response rate and to prolong survival with durable remission, for example, by the placement of an Ommaya reservoir (3), by intravenous methotrexate (9) and by concurrent or sequential radiation therapy and systemic chemotherapy. Trials of combination regimens of intrathecal chemotherapy with methotrexate and other drugs, such as ara-C and thiotapec, have also been conducted.

In our study, the cytological response rate and overall survival were higher in the combined (MHA) treatment arm than in the single (M) arm in patients of LMC without symptomatic areas or mass lesions on neuroimaging studies. The difference in survival could be mainly due to the difference in the numbers of cytological responders among those who did not receive irradiation (M vs MHA: 2/16 vs 7/12). There was no difference in the numbers of responders in patients irradiated (M vs MHA: 2/13 vs 3/14). Despite the limitation of a retrospective study, this result is worthy of consideration. The addition of ara-C to a methotrexate-based regimen has shown the possibility of improving the efficacy of intrathecal chemotherapy for LMC in solid tumors, especially in LMC patients without symptomatic areas or mass lesions on neuroimaging studies. Although the cytological response rate to the combination therapy is encouraging, the superiority should be suggested prudently when the neurological response rate and the survival duration were not improved in the responders.

Previous attempts to combine ara-C with methotrexate in intrathecal chemotherapy have failed to prove the benefit of the regimen. Giannone et al. (3) reported the treatment results for 22 patients with meningeal neoplasm of breast cancer, lung cancer and malignant glioma. The simultaneous triple-drug intraventricular chemotherapy consisting of methotrexate, cytosine arabinoside and thiotapec caused unacceptable myelosuppression without increasing the response rate, response duration or survival, when compared with single-agent methotrexate and radiotherapy. Hitchins et al. (4) reported that the response to methotrexate alone was superior to that to combined methotrexate and ara-C, but not significantly so (61 vs 45%, \( P > 0.10 \)) in a prospective randomized study of 44 patients mainly composed of small cell carcinoma and breast carcinoma.

Hitchins et al.’s prospective randomized trial (4) and Wasserman et al.’s analysis of 90 patients (1) included some patients who were clinically suspected of having LMC based on the abnormalities of neurological findings and imaging studies without pathological confirmation. In Hitchins et al.’s trial, the CSF cytology of 11 (25%) patients was negative. In our study, we confined the inclusion criteria to histologically confirmed LMC and the definition of the response was based on the pathological change, namely the clearance of malignant cells from the CSF. The differences in the eligibility criteria and the definition of response might have led to the different results. When a response was merely judged by the neurological response as in the previous studies, the two arms in our study showed no difference in the response rate (M vs MHA: 58.6 vs 73.1%, \( P = 0.260 \)), which is consistent with the previous studies.

The histological composition of patients in our study was different from that in the previous ones. In Grossman and Krabak’s randomized trial (7), 10 patients (19%) with lymphoma were included, which were more responsive to chemotherapy than other types of solid tumor. Hitchins et al.’s trial included 13 (29%) patients with small cell lung carcinoma and 11 (25%) patients with breast cancer, while the histology of the remaining patients was diverse (9% CNS primary, 7% non-small cell lung cancer, 7% lymphoma and some cases of melanoma and nasopharyngeal carcinoma). In our study, the histology of 82% patients was adenocarcinoma. Such homogeneity in the histology of our patients might make our results different from those of the previous studies. It is demonstrated by the result that the median survival of the MHA arm was also longer than that of the M arm (23.9 vs 10.4 weeks, \( P = 0.038 \)) in patients with adenocarcinoma of the lung in the subgroup analysis. This improvement in survival with combination chemotherapy deserves to be noted, as adenocarcinoma is a less sensitive tumor and shows unsatisfactory results with intrathecal chemotherapy.

Even though the five patients with small cell lung carcinoma were excluded from the analysis, the response rate of the MHA arm exceeded that of the M arm (27.3 vs 14.3%, \( P = 0.302 \)), but did not reach significance. We think that the disappearance of statistical significance is partially due to the reduction in the number of patients and the contribution of the patients with small cell lung carcinoma to the response rate of the MHA arm might be significant. Moreover, the superiority of the com-
bination treatment was not proven in a multivariate analysis. Therefore, it needs to be discussed cautiously whether the combination regimen is more beneficial for the response rate and survival in solid tumor LMC.

The adverse effects encountered in the two treatment arms were not so severe as to require discontinuation of the intrathecal treatment. The incidence and degree of side effects were not different significantly between the two arms. A series of previous studies also found that the addition of other drugs to a methotrexate single regimen did not increase neurological or systemic toxicities (4). Even in a trial of a combined regimen consisting of methotrexate/ara-C/thiotepa (3), no unusual or severe toxic conditions were observed, although the drugs were co-administered at full doses.

We selected ara-C as an add-on agent with methotrexate in our study. Although ara-C has been thought to be ineffective as part of systemic combination chemotherapy in patients with non-lymphomatosus solid tumors, few effective additive agents except ara-C in the intrathecal treatment of LMC were available at the start of this study.

Ara-C has not been considered for the intrathecal chemotherapy of LMC in solid tumors, mainly because the combination treatment was not more effective than the single regimen treatment in a few randomized prospective trials. However, ara-C is an easily available and tolerable antineoplastic drug. In our study, the addition of ara-C made a noticeable improvement in the cytological response of malignant cells and the overall survival without increasing significant adverse effects. Therefore, we think that the possibilities of a combination regimen including methotrexate and ara-C should be reassessed carefully. The absence of an alternative neoplastic drug which is easily available at present also makes this suggestion reasonable. Recently, the promising results of a study using sustained-release cytarabine (10) give indications as to the effectiveness of ara-C in solid tumor LMC.

In conclusion, the addition of ara-C to methotrexate showed greater effectiveness than methotrexate single regimen for intrathecal chemotherapy of solid tumor LMC in our study, which was discordant with the results of previous randomized prospective studies. We suggest that this discrepancy is due to the differences in the response criteria and the population characteristics. We therefore recommend that a further randomized prospective comparison should be performed for combination versus single regimen intrathecal chemotherapy for patients with homogeneous characteristics to prove the possible superiority of the combination regimen of ara-C and methotrexate over the single regimen, as shown in this study.

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References