CASE REPORT

Exploring the possibility of intravenous modified high dose methotrexate in leptomeningeal metastatic disease treatment: A case series

Sin Pei Tan, MBBS[1], Hui Li Lim, MBBS[2], Nurul Huda Binti Razali, MBBS[2], Chun Sen Lim, MCO[1]

[1]Oncology and Radiotherapy Department, Hospital Sultan Ismail, Ministry of Health Malaysia, [2]Clinical Research Centre, Hospital Sultan Ismail, Ministry of Health Malaysia.

SUMMARY

Leptomeningeal metastatic disease (LMD) is a rare complication of advanced cancer, with no standard management and often associated with poor prognosis and short survival time. Current treatment options involve high doses of intravenous (IV) or intrathecal (IT) methotrexate (MTX), which can be associated with significant side effects. To mitigate the adverse effects, this case series aims to highlight the feasibility a reduced IV MTX dosage, which we termed "IV modified high dose MTX" to treat LMD. In the three cases of LMD with underlying breast cancer, we reduced the IV dosage of MTX to 2.5-3 g/m^2 (standard high dose MTX is 3-3.5 g/m^2) and examined the outcomes of clinical symptoms, side effects and overall survival of the patients. In the three LMD cases, the use of IV modified high dose MTX had reduced toxicity, improved neurological symptoms, partially recovered the quality of life, and conferred a survival duration comparable to the conventional high-dose regime. Given the favourable safety profile and comparable treatment effect, our case series highlighted the importance of further investigation to establish the optimal dosing regimen of MTX in the palliative care of LMD.

INTRODUCTION

Leptomeningeal metastatic disease (LMD) is characterised by cancer metastasis to the subarachnoid space in between the pia and arachnoid maters of the brain. Melanoma, breast and lung cancers are common primary tumour origin of LMD.[1,2] It occurs in about 5% of advanced breast cancer with an overall survival of three to four months.[1] Triple negative breast carcinoma, old age, presence of brain metastases and low albumin have been associated to a poorer prognosis.[3]

Symptoms of LMD vary between patients and largely depend on the anatomical site of the metastatic cells. The symptoms develop either due to the obstruction of cerebrospinal fluid (CSF) flow, increased intracranial pressure or direct infiltration of tumor cells. Common manifestations include seizure, headache, nausea, impaired consciousness, radicular pain due to the involvement of spinal roots, or a focal neurological deficit if the cancer cells have infiltrated into the brain parenchyma.[4]

The gold standard of LMD diagnosis remains the demonstration of tumor cells in CSF. The test has an underwhelming sensitivity. Repeating the test up to 3 times may increase its sensitivity beyond 90%.[5] Magnetic resonance imaging scan with gadolinium contrast has become a reliable tool for LMD diagnosis. There is no standard treatment for LMD. Mainstream therapies include focal radiotherapy and chemotherapy with high-dose methotrexate (HD MTX), but for the latter, the optimal administration route either via intrathecal (IT) or intravenous (IV) remains highly debatable. IT MTX is conventionally used, but its effectiveness depends on a good CSF flow and the adverse reactions are significant, leading to the increased popularity of IV HD MTX. As most LMD patients eventually succumb to the disease, current treatment strategies aim to prolong survival and improve quality of life by stabilizing and delaying neurological deterioration. Given the palliative nature of the treatment approach, it is possible to further reduce the dosage of IV MTX if it can minimise the side effect without comprising the drug efficacy. Here, we would like to showcase three patients with LMD originated from breast carcinoma and discuss the possible improvement on the chemotherapy strategies by reducing the systemic dosage of MTX, which we termed "IV modified high dose MTX".

CASE REPORT

Case 1

The patient was a 58 years old Chinese female diagnosed with right breast carcinoma in 2013 and treated with right mastectomy and axillary clearance. Histopathology examination (HPE) demonstrated a stage 3A, T2N3 invasive lobular carcinoma, ER+, PR+, and HER2-. She underwent 6 cycles of chemotherapy comprised of 3 cycles 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) and 3 cycles of Docetaxel followed by adjuvant radiotherapy. Upon completion, she was treated with Tamoxifen since November 2013. The patient had been in remission until December 2019, when she developed headache and vomiting. A magnetic resonance imaging (MRI) showed multiple tiny low signal modules that scattered in T2-T11, which confirmed leptomeningeal metastasis. Bone metastases at T2 and T7 were also noted. The patient received palliative radiation to the spine and started on Letrozole and Palbociclib. The symptoms worsened in September 2020 and a restaging imaging demonstrated a progressive leptomeningeal carcinomatosis with gadolinium enhancement. She remained Eastern Cooperative Oncology Group performance

This article was accepted: 29 April 2023
Corresponding Author: Lim Hui Li
Email: huililim1191@gmail.com

status (ECOG) 1 with Karnosky performance status (KPS) grade 90. Lumbar puncture with cerebrospinal fluid (CSF) cytology analysis was positive for metastatic breast cancer, positive for ER, negative for PR and HER/neu IHC stain. She received 8 cycles of IT MTX, which was 12mg twice weekly for 4 weeks, followed by 12mg once weekly for 4 weeks. Repeated cerebrospinal fluid cytology in January 2021 showed no malignancy cell. However, the disease continued to progress with worsening of headache and left-sided body weakness in February 2021. Her performance status deteriorated to ECOG 3 (KPS grade 50). She then received 5 cycles of systemic chemotherapy with IV modified high dose MTX administered 2 weekly. The dosage ranged from 2.5-3 g/m^2, with the first two cycles (C1 and C2) using 2.5 g/m^2, the third cycle (C3) using 2.8 g/m^2, and the fourth cycle (C4) using the maximum dose of 3 g/m^2. She was able to tolerate the regime relatively well without significant complications. At the point of writing, her condition stabilized at ECOG 3 (KPS grade 50). Symptoms like vomiting and pain improved after the first cycle of IV MTX. The patient survived 8 months with good quality of life. Subsequently, she defaulted the follow up.

Case 2

A 60 years old female with hypertension, type II diabetes mellitus and dyslipidemia was diagnosed with metastatic right breast invasive lobular carcinoma, pT3N3M1(bone), triple negative disease, underwent right mastectomy and axillary clearance (MAC) followed by adjuvant chemotherapy and radiotherapy which were completed in 2016. In October 2020, she presented with generalized body weakness, vomiting and headache. She had bilateral eyes optic disc swelling with bilateral 6th nerve palsy, facial asymmetry and reduced power of all limbs. Contrast enhanced computed tomography (CECT) brain showed chronic ischaemic changes with no brain lesion. MRI brain showed an empty sella sign with no obstructive hydrocephalus. Computed tomography (CT) of the thorax, abdomen and pelvis showed no other new visceral metastasis. A lumbar puncture analysis was unremarkable. The patient was referred to neuromedical team for further investigations. Her condition deteriorated to ECOG 2 (KPS 70) in November 2020 with worsened headache, vomiting, neck stiffness, blurring of vision, seizure. Repeated lumbar puncture revealed occasional atypia cells characterised by cells with eccentric nuclei and large rounded nuclei and moderate amount of cytoplasm. Her MRI brain and neck revealed multiple tiny nodules in the cervical vertebral bodies. Together, the results were suggestive of LMD. She was treated with IV MTX (2.5 g/m^2) administered 2 weekly in December 2020. The dose was gradually increased to 3 g/m^2 during the third cycle of chemotherapy. However, the chemotherapy caused grade 3-4 toxicity, including myelosuppression, elevated serum hepatic transaminases and prolonged MTX clearance. The highest alanine transaminase (ALT) and alkaline phosphatase (ALP) levels recorded exceeded the upper limits by 3 and 1.5 times, respectively. Due to the severe side effects, her chemotherapy was deferred multiple times, and the interval of her chemotherapy regime was prolonged to once in every 3 weeks with a dose reduction to 2.8 g/m^2. Post cycle 4 IV MTX, an improvement in performance status to ECOG 1 (KPS 80) was noted. Repeated CSF was free of atypia cells. However, her liver function test remained deranged and the typical side effects of MTX persisted. She completed a total of 7 cycles of IV MTX by April 2021. CT imaging post chemotherapy showed an overall stable disease with diffuse nodular leptomeningeal enhancement through the cauda equina. Nonetheless, her condition deteriorated in May 2021 with cord compression symptoms and ECOG 3 (KPS 40). MRI spine confirmed disease progression. She was then started on palliative hormonal therapy letrozole. The patient transitioned to end-of-life care and died in August 2021. The patient lived a total of 9 months after the initial diagnosis of LMD.

Case 3

A 62 years old Malay lady was diagnosed with metastatic right breast invasive carcinoma, pT3N0cM1 (lungs-small volume, bone), triple negative disease. She underwent right mastectomy and axillary clearance and adjuvant anthracycline-based chemotherapy followed by radiotherapy in 2016. In November 2019, she complained having progressive bilateral limb weakness. MRI spine showed a conus medullary lesion. She then underwent laminectomy and excision of the lesion. HPE showed malignant spinal cord tumour consistent with breast metastasis. Five fractions of palliative radiotherapy to the spine were given in December 2019. The tumour recurred 2 months later and re-excision was done. HPE was consistent with the previous disease. She completed 6 cycles of chemotherapy Paclitaxel in July 2020. Positron emission tomography (PET) scan in December 2020 showed a new ^{18}F-fluorodeoxyglucose avid enhancing lesion at T12/L1 level, measuring 0.94cm x0.72cm, highly suspicious of metastasis, with no other visceral metastasis. CSF analysis found no malignant cells. However, in view of recent radiotherapy treatment received, patient was suggested to commence on 3 weekly chemotherapy MTX in January 2021. She received total 5 cycles of IV MTX ranging from 3-3.5 g/m^2. However, treatment was frequently delayed due to recurrent urinary tract infections. Her ECOG status remained stable (ECOG 3, KPS 50) throughout the treatment. Repeated PET CT imaging post cycle 5 IV MTX noted worsening spine metastasis characterized by larger and more intense lesion extending from T9 to L1. Palliative therapy with Eribulin was given to the patient and discontinued at Cycle 5 due to intolerance. Her disease has been under controlled for 7 months since the initial diagnosis of LMD.

DISCUSSION

Our case series highlight two aspects in the treatment of LMD: (1) the tolerability and efficacy of IV MTX and (2) the optimal dosage of IV MTX for LMD originated from breast carcinoma. All our LMD patients were treated with IV modified high dose MTX which was well-tolerated, effective and able to maintain quality of life. Conventionally, IT MTX is the primary therapy although its efficacy compared to systemic chemotherapy is not well-established. IT MTX causes significant neurotoxicity especially when CSF flow is obstructed, thus limiting its use in patients with bulky LMD, hydrocephalus and dural-based or parenychemal disease. The administration of IT MTX is an invasive procedure and highly operator dependent which can be associated with procedural complications such as meningitis, myelopathy,

myelosuppression, encephalopathy.[2] In contrast, IV HD MTX has increasingly used due to its convenience, high tolerability and ability to attain good serum and CSF cytotoxic levels.[6] In line with our cases, the effectiveness of IV HD MTX in LMD originated from breast carcinoma has been previously reported.[7-9]

The optimal MTX dose, infusion duration and leucovorin rescue of IV regimen are disease- and protocol-specific. Most studies utilised an IV HD regime of 3-3.5 g/m^2 of MTX fortnightly which can achieve comparable or even higher CSF concentration than IT administration.[6] In two larger series, the rate of stable disease ranged from 30 to 45%, with a median survival of five to six months.[7,10] Similarly, Glanz et al. (1998) reported a median survival of 13.8 months with IV HD MTX versus 2.3 months with IT MTX.[6] CSF and serum MTX concentrations were maintained at a cytotoxic level much longer than with IT dosing.[6] Cytologic clearing was seen in 81% of patients compared with 60% of patients treated intrathecally. Prolonged survival has also been described in many reports.[7-9] Here, we used a stepwise increment of IV modified high dose MTX ranging from 2.5-3.5 g/m^2. The regimen was adequate to stabilize the patients' condition for up to 7 months before any major disease progression was detected. At the time of penning down this report, all the patients are still alive, translating to a survival period of at least 9 months. The observations are in line with the overall survival (0.7 – 33.9 months) of IV HD MTX-treated LMD patients7 and was much longer than those receiving IT MTX (2.3 months) as reported by Glanz et al. (1998)[6]. Hence, our cases are supportive to the use of IV modified HD MTX in LMD, especially those originated from the breast carcinoma.

Low toxicity is a key advantage of IV modified HD MTX. We observed that a slightly lower of at 2.5-3 g/m^2 of IV MTX fortnightly demonstrated good tolerability and minimal toxicity. The therapeutic effect was not compromised by the dose reduction. Likewise, according to Bazan et al (2019), a dosage of 3 g/m^2 of systemic IV HD MTX demonstrated an acceptable toxicity profile without compromising efficacy.[10] In contrast, the typical IV HD MTX may cause significant hepatotoxicity. Elevated serum ALT or AST are observed in 15-50% of the patients receiving IV HD MTX. In view of the better safety profile and comparable efficacy, further investigations on the use of 2.5-3 g/m^2 of IV MTX, especially in high-risk patients, are warranted.

Among the three patients, Case 2 exhibited the least favourable outcome. There was a significant gap (2 months) to acquire her diagnosis because her CSF analyses were repeatedly negative. False negative of the test is not uncommon.[5] Hence, a negative result is insufficient to exclude LMD and repeated test is highly recommended especially when the clinical presentations align well with the diagnosis. CT and MRI are the alternative diagnostic tools. Scanning the brain and whole spine should be performed as LMD can affect any part of the central nervous system.[5] In Case 2, only MRI brain was performed at the early course of the investigation. The false negative result from CSF analysis and incomplete imaging result significantly impeded the diagnosis process. The patient also exhibited poorer performance status and was unable to tolerate the chemotherapy, necessitating modification of the chemotherapy regime. These reasons could contribute to the poor clinical outcome.

LMD is often associated with poor prognosis. Without any treatment, the estimated survival after diagnosis is 6 to 8 weeks. This is prolonged to 8 to 30 weeks in treated cases8.Recent advancements in the targeted therapy of different breast cancer subtypes may further improve the outcome of LMD with underlying breast cancers. For instance, cyclin-dependent kinase (CDK) 4/6 inhibitors such as Abemaciclib and Palbociclib and Poly (ADP-ribose) polymerase (PARP) inhibitors Olaparib and Talazoparib have demonstrated promising intracranial activities in hormone positive Her^2 negative breast cancers and triple negative breast cancers, respectively.[11-14] Larger trials are warranted to examine their feasibility in LMD with underlying breast cancers of the corresponding subtypes. In our case series, the mean period from diagnosis to disease progression were more than 24 weeks. Two of the patients were able to tolerate IV modified high dose MTX of 2.5-3 g/m^2, which conferred lower toxicity, higher tolerability and comparable survival duration to the HD counterpart. The favourable outcomes highlight its feasibility to treat LMD and hence, further investigation to optimize the dosage of IV MTX is pertinent.

CONCLUSION

In conclusion, IV MTX could be a better alternative to the IT counterpart for the therapy of LMD originated from breast carcinoma. The possibility to use IV modified high dose MTX of 2.5-3 g/m2 should be investigated in view of better tolerability and comparable therapeutic efficacy.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

DECLARATIONS

The investigators declare no conflict of interest. Informed consent was obtained from all patients/patients' family members in line with COPE standards.

REFERENCES

1. Le Rhun E, Preusser M, van den Bent M, Andratschke N, Weller M. How we treat patients with leptomeningeal metastases. ESMO Open. 2019; 4(Suppl 2): e000507.
2. Abu Hejleh T, Clamon G. Advances in the systemic treatment of leptomeningeal cancer. Clin Adv Hematol Oncol. 2012; 10(3): 166-70.
3. Kingston B, Kayhanian H, Brooks C, Cox N, Chaabouni N, Redana S, et al. Treatment and prognosis of leptomeningeal disease secondary to metastatic breast cancer: A single-centre experience. Breast. 2017; 36: 54-9.
4. Zairi F, Kotecki N, Rodrigues I, Baranzelli M-C, Andre C, Dubois F, et al. Prospective follow-up of a cohort of 112 patients with leptomeningeal metastases of breast cancer recruited from 2007 to 2011: Prognostic factors. Journal of Clinical Oncology. 2012; 30(15_suppl): 2070-.

5. Parker N, Dilling M, Lalich D. Leptomeningeal Carcinomatosis: Challenges in Diagnosis and Treatment. Annals of Clinical Case Reports. 2020; 5(1): 1837.
6. Glantz MJ, Cole BF, Recht L, Akerley W, Mills P, Saris S, et al. High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: is intrathecal chemotherapy necessary? J Clin Oncol. 1998; 16(4): 1561-7.
7. Lassman AB, Abrey LE, Shah GD, Panageas KS, Begemann M, Malkin MG, et al. Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol. 2006; 78(3): 255-60.
8. Kapke JT, Schneidewend RJ, Jawa ZA, Huang CC, Connelly JM, Chitambar CR. High-dose intravenous methotrexate in the management of breast cancer with leptomeningeal disease: Case series and review of the literature. Hematol Oncol Stem Cell Ther. 2019; 12(4): 189-93.
9. Santa-Maria CA, Cimino-Mathews A, Moseley KF, Wolff AC, Blakeley JO, Connolly RM. Complete radiologic response and long-term survival with use of systemic high-dose methotrexate for breast cancer-associated leptomeningeal disease. Clin Breast Cancer. 2012; 12(6): 445-9.
10. Bazan F, Dobi E, Royer B, Curtit E, Mansi L, Menneveau N, et al. Systemic high-dose intravenous methotrexate in patients with central nervous system metastatic breast cancer. BMC Cancer. 2019; 19(1): 1029.
11. Tolaney SM, Sahebjam S, Le Rhun E, Bachelot T, Kabos P, Awada A, et al. A Phase II Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor-Positive Breast Cancer. Clin Cancer Res. 2020; 26(20): 5310-9.
12. Brastianos PK, Kim AE, Wang N, Lee EQ, Ligibel J, Cohen JV, et al. Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations. Nat Cancer. 2021; 2(5): 498-502.
13. Exman P, Mallery RM, Lin NU, Parsons HA. Response to Olaparib in a Patient with Germline BRCA2 Mutation and Breast Cancer Leptomeningeal Carcinomatosis. NPJ Breast Cancer. 2019;5:46.
14. Pascual T, Gonzalez-Farre B, Teixido C, Oleaga L, Oses G, Ganau S, et al. Significant Clinical Activity of Olaparib in a Somatic BRCA1-Mutated Triple-Negative Breast Cancer With Brain Metastasis. JCO Precis Oncol. 2019; 3: 1-6.