Case Report

Chemotherapeutic Strategy Treatment of Brain Metastases from Lung Cancer through Antiangiogenesis Mechanism

Masato Hada[1], Abid Rashid[2], Muhammad Akram[3*], Umme Laila[1], Rida Zainab[3], Momina Iftikhar[3], Sundus Saleem[3], Gaweł Sołowski[4], Walaa Fikry Elbossaty[5], Fethi Ahmet Ozdemir[4], Pragnesh Parmar[6]

[1]Hada Clinic, 1728-2 Oooka Numazu-City, Shizuoka 410-0022, Japan
[2]Faculty of Medical Sciences, Government College Ucniversity Faisalabad, Pakistan
[3]Department of Eastern Medicine, Government College University Faisalabad, Pakistan
[4] Department of Molecular Biology and Genetics, Faculty of Science and Art, Bingol University, Bingol, 1200, Türkiye.
[5] Department of Biochemistry, Damietta University, Egypt
[6]Additional Professor and HOD, Forensic Medicine and Toxicology, AIIMS, Bibinagar, Telangana, India
[*]Corresponding author email: **makram_0451@hotmail.com**

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Abstract

In some cases brain metastases arise from non-small cell lung cancer, and chemotherapy has been used for long periods in the treatment of these cases, but its effectiveness has not been proven due to its weak effect in addition to its deadly toxic properties. Therefore, there was a need to search for appropriate therapeutic means for these cases, so work was done on vascular endothelial growth factor, which has an important role in the development of the disease. Where it was used against those blood vessels, either alone or combined with drugs toxic to cancer cells. One of the most important enzymes that play an important role in the formation of brain edema is cyclooxygenase (COX) -2, through its role in the production of PGE2 production. Therefore, COX-2 inhibitors are used in the

treatment of brain tumors. In this report, a case will be presented of a patient with lung cancer, in addition to having brain metastases, who was treated with radiotherapy and chemotherapy. Gemcitabine, thalidomide, and celceoxib were added to the treatment protocol and by examining the patient it was found that he had completely recovered from brain metastases. Therefore, this protocol is recommended in the treatment of these patients.

Key words

Non-small cell lung cancer, Radiotherapy, Chemotherapy, COX-2 inhibitors, Gemcitabine, Thalidomide, Celecoxib, Brain metastases.

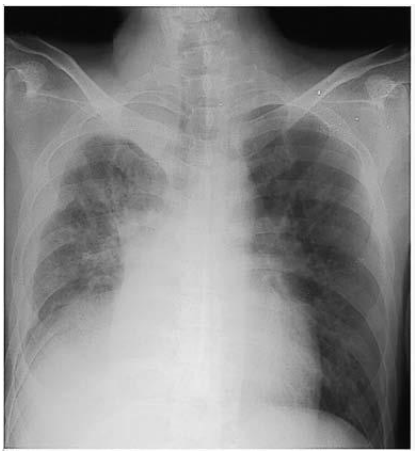
Introduction

The main strategy for treating brain metastases is radiotherapy and surgical intervention. However, chemotherapy is used in special cases, and it has been noted that some of the drugs that are used in those cases are used to treat side effects, such as the use of glucocorticoids in the treatment of brain edema after direct exposure to radiation. And since some research confirmed the effectiveness of using antiangiogenesis in influencing the blood vessels feeding those cancer cells, and then leading to an improvement in the patient's condition. Among these drugs is Thalidomide, which is currently used in the treatment of brain tumors, due to its effectiveness in that it acts as anti-VEGF, anti-FGF, and anti-TNF-α, which is antiangiogenesis and thus leads to an improvement in the patient's condition. Also, celecoxib is a cyclooxygenase（COX）-2 inhibitor and works to inhibit the production of prostaglandin, thus improving brain edema. Gemcitabine also inhibits NF-kB. Therefore, when using a treatment protocol consisting of Thalidomide, celecoxib, and gemcitabine in the treatment of lung cancer and brain metastases, it was observed that the condition was completely cured, improved, and the patient's life was prolonged.

Case report

The case is a 36-year-old Japanese national who was diagnosed with brain metastases after suffering from lung cancer. In August 2002, he underwent a right and median lobectomy as a result of lung cancer. The case was diagnosed as poorly differentiated non-small-cell lung cancer. The patient was subjected to the carboplatin and paclitaxel treatment protocol. In January 2003, after the end of chemotherapy, the patient began to complain of shortness of breath, headache, and vomiting. X-rays were done on the brain to find out the causes of these symptoms, and it was found that the patient had multiple brain metastases. The patient underwent radiotherapy and chemotherapy, where a temporary improvement occurred immediately, followed by a feeling of tingling, nausea and headache. In February, the laboratory examination was found to be good except for CEA which was 14.8 ng/ml. Throughmake a chest x-ray, it was found that on the first day, shrinking right lung volume and enlarged lymph nodes (1^{st} day) (**Figure - 1A**), On day 75, accumulation of pericardial effusion and contraction of the lower section of the right lung was revealed, (**Figure - 1B**).

Figure – 1A: X-ray Chest appear shrinking right lung volume and enlarged lymph nodes (1^{st} day). **1B:** X-ray Chest Accumulation of pericardial effusion and contraction of the lower section of the right lung (75 day).



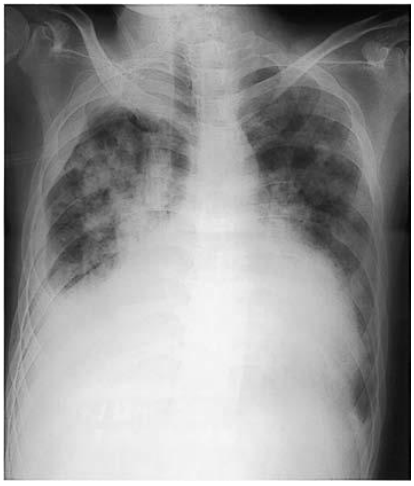


Figure – 2: Brain MRI appeared ring-shaped metastatic lesions in the cerebral and cerebellar hemispheres. This lesions have minimized through chemotherapy (A: day 1, B: day 35, C: day 43, D: day 70).

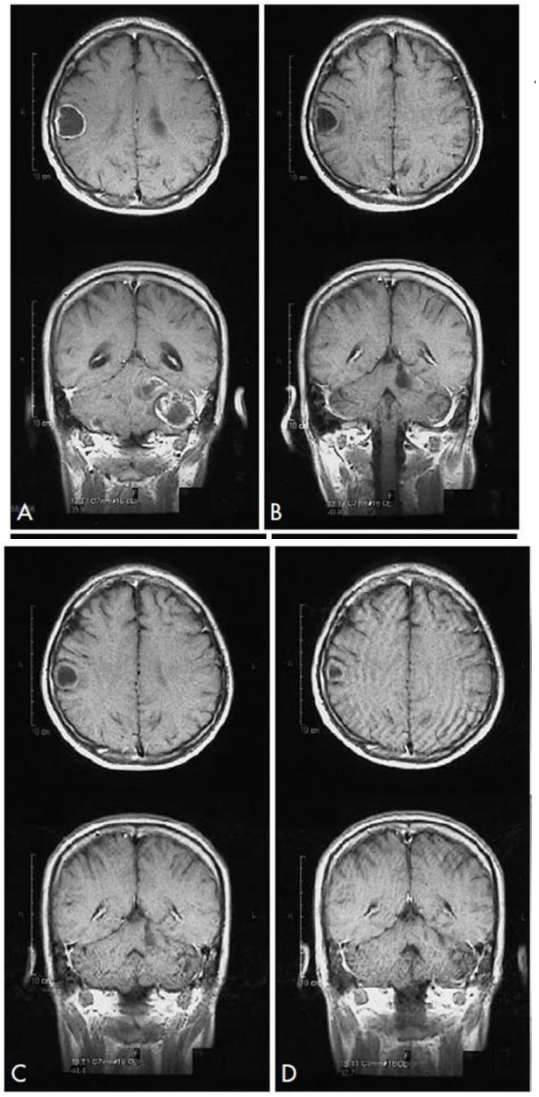
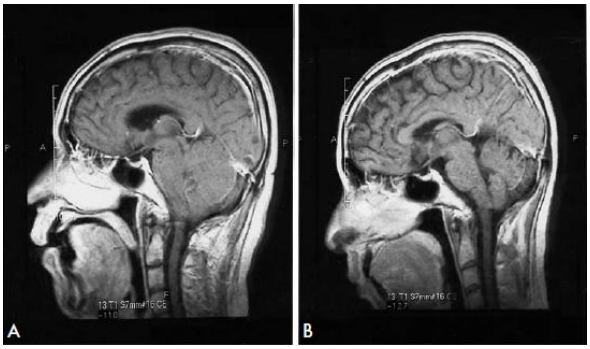


Figure – 3: A and B show disappearance of brain edema (A: day 2, B: day 54).



The brain's MRI imaging revealed metastatic lesions (**Figure - 2**) and cerebral edema in the cerebral and cerebellar hemispheres (**Figure - 3**).

A treatment protocol was included mixing of three types of chemical drugs, namely thalidomide, celecoxib, and gemcitabine together, side by side.

The treatment plan started from the first day by giving thalidomide 300 mg/day with celecoxib 600 mg/day every day, and on the tenth day gemcitabine 1 g was added to be given every ten days.

On the 16th day, an improvement in the clinical functions of the patient was observed, as he excreted approximately 10,000 ml of urine over two days, and the specific gravity was 1.031. The symptoms that the patient was suffering from upon admission to the hospital, such as headache, vomiting, dizziness, and nausea, improved.

The resonance was repeated on the brain to follow up on the condition of the tumor, and the surprise was that the metastatic lesion decreased (**Figure - 2**) and the cerebral edema disappeared (**Figure - 3**). Unfortunately, there was an exacerbation of pulmonary lesions, and in May 2003 the patient died as a result of pulmonary failure.

Discussion

Angiogenesis is one of the ways in which cancer cells can obtain food for growth and division.

Angiogenic factors including VEGF, FGF, COX-2 and TNF-α play an important role in this process. Thalidomide has an important role in stopping this process by inhibiting mRNA encoding angiogenic factors [2].

When Thalidomide inhibits TNF-α, it reduces the patient's appetite and improves his vital functions. VEGF promotes the growth of cancer cells in brain metastasis. Thus, the antagonistic effect of Thalidomide on TNF-α and VEGF improves brain metastasis [3].

In addition to Cyclooxygenase (COX) -2 has an effective role in the process of carcinogenesis, as it helps cell proliferation, angiogenesis, through the production of PGE 2, which causes cerebral edema. Celecoxib is used as an anti-Cyclooxygenase, so it is used in the treatment of cerebral edema [4, 5].

Gemcitabine also works to stop the formation of DNA during the elongation process, and this works to stop the growth of cancer cells, in addition to encouraging the process of programmed cell death by stopping the G1 / S-phase [1].

Conclusion

Research has confirmed that patients with brain tumors can survive a period not exceeding 3-4 months after radiotherapy and chemotherapy.

The patient was subjected to a treatment protocol that included mixing a group of chemical drugs, after obtaining informed consent as repentance from the patient's family members.

It was noted that the use of thalidomide and celecoxib in addition to gemcitabine worked to improve the patient's condition, the disappearance of cerebral edema and the shrinkage of the tumor size. Unfortunately, however, there was a relapse and deterioration in the patient's condition, and as a result of pulmonary failure, the patient died.

However, through research it was found that treatment with thalidomide and celecoxib, and gemcitabine has an effective effect in the treatment of brain metastasis and cerebral edema, although it was not effective in treating lung cancer.

Therefore, it is recommended to add thalidomide, celecoxib, and gemcitabine to the treatment protocol for patients with brain metastasis.

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