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Case Report
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Weekly Low Dose Pemetrexed for an Elderly Advanced Lung Adenocarcinoma Patient Who had Failed First-Line Chemotherapy and EGFR-TKIs: A Case Report

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Abstract

Elderly advanced lung adenocarcinoma patients, especially those who failed first-line chemotherapy and EGFR-TKIs, can hardly receive conventional chemotherapy. A 71-year-old woman suffering from such situation with lung adenocarcinoma of stage IV received a total of 62 times weekly low dose pemetrexed therapy (200mg, qw) intermittently and resulted in dramatically tumor response. It is well tolerated. Weekly low dose pemetrexed might be suitable for EGFR-TKIs resistant elderly advanced lung adenocarcinoma patients.

Keywords: Pemetrexed; Low dose; Weekly therapy; Lung adenocarcinoma

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Background

Lung cancer has been the most lethal of all neoplasm so far, especially among women in China, of which the majority is non-small cell lung cancer (NSCLC) [1,2]. More than 40% lung cancer patients are diagnosed over 70 years old [3]. Most of them have lost the operative opportunity. Chemotherapy is once the mainly treatment for advanced NSCLC. Epidermal growth factor receptor tyrosine kinase inhibitors(EGFR-TKIs), such as erlotinib and gefitinib, are the most effective medicines throughout the first-, second-line therapy and maintenance therapy, especially for those with favourable clinical features such as female, non-smoker and adenocarcinoma [4-6]. Treatment with EGFR-TKIs has improved progression-free and overall survival in patients, particularly those who have EGFR mutations. NSCLC harboring activating mutations of EGFR are particularly sensitive to TKIs. However, most patients inevitably might be confronted with TKIs resistance. What can we do when the elderly advanced NSCLC patients have failed first-line chemotherapy and EGFR-TKIs, especially those who cannot afford gene test and other targeted drugs? Although there are some researches on this field [7,8], there is no standard treatment.

Furthermore, most of these clinical data are obtained from the younger population. Numerous prospective and retrospective studies have concluded that elderly patients achieve a similar survival benefit from first-line chemotherapy of advanced NSCLC compared with their younger counterparts [9]. But elderly patients tend to have more toxic side effects and cannot tolerant to these conventional medical treatments than their younger counterparts, especially when they failed first-line therapy [10]. Therefore, clinical data obtained from the younger patients cannot be applied to the elderly patients rigidly. Based on phase II/III trials, single chemotherapy with third-generation agent (gemcitabine) is to be supposed as the standard treatment for elderly advanced NSCLC patients [3]. Pemetrexed has similar curative effects with gemcitabine and lower side effects, but there's no data about pemetrexed in these patients, especially those without good performance status. The following case shows the effective treatment.

Case Presentation

On 20th Jul. 2009, a 71-year-old Chinese woman consulted our department complaining of progressively worsening fever (38°c), cough, chest pain, a feeling of bone pain in the hip, legs, and emaciation. The height of the patient was 164cm and the weight was only 35Kg. She was diagnosed by CT (left apical lung, nodular, 6x5cm) and aspiration biopsy of lung in 2008. Pathologic examination of the biopsy specimen shows adenocarcinoma. She refused operation and only received two cycles of chemotherapy with paclitaxel and carboplatin after biopsy. As the disease progresses, she took gefitinib during the next six months without gene test. She was diagnosed by ECT of multiple bone metastasis (ilium, legs, knee-joint and ankle cannot flex) in Apr. 2009. Local radiotherapy

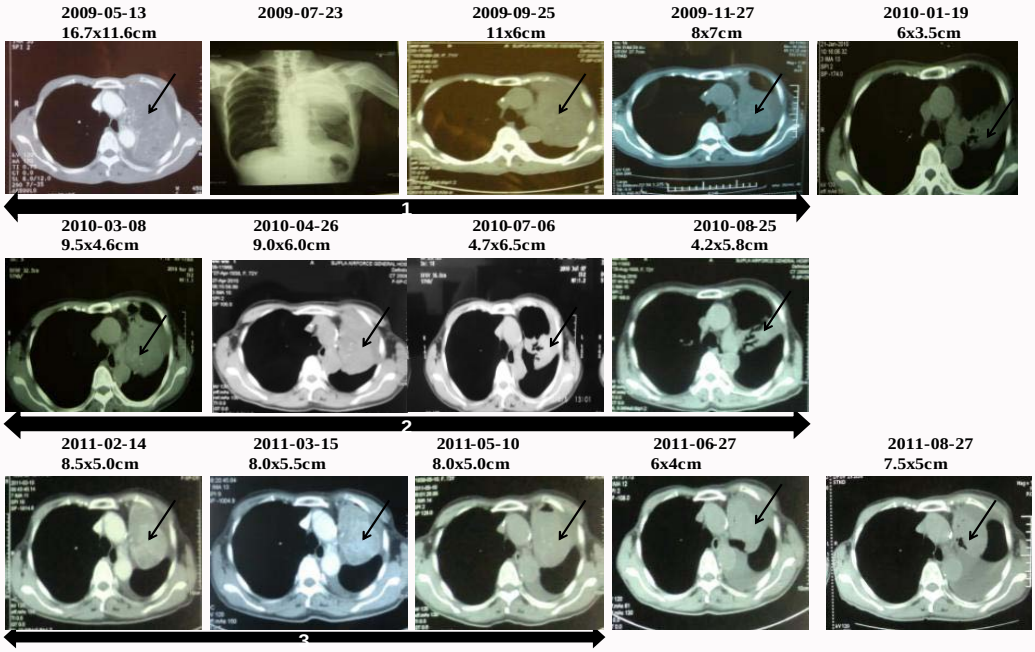

Figure 1: The change of left apical lung nodule during therapy.

was performed before she decided not to receive treatment any more except oral analgesia. Until May. 2009, the tumor was found increased to 16.7X11.6cm with intrapulmonary multiple nodules (stage T4N2M1-IV) by CT. By the time, she tried to receive weekly low dose pemetrexed (200 mg, qw, 28d as one cycle) therapy with Karnofsky performance score (KPS) 60 and pain score 7. One cycle later, her symptoms was alleviated, such as cough times decreased, knee joint flexed, joint pain relieved, and 0.5 Kg of weight gained, KPS increased to 80 and pain score 4. After four cycles, her weight was increased to 45 Kg. She was able to ambulate without any assisted device and could perform daily activities independently with KPS 100 and pain score 0. During the first four cycles, treatment was suspended once for the WBC decreased to $3.5x10^9$/L, CT was performed to confirm the curative effect, the tumor shrunk to 6x3.5cm. Then we decided to have a break because she was diagnosed with partial remission.

The patient consulted our department the second time for CT showed left lung tumor had increased to 9.5x4.6 cm, accompanied with tumor marker being increased on 8th Mar. 2010. Then she received four and half cycle (18 times) low dose weekly pemetrexed therapy. During this period, chromatosis appeared on the facial skin and limbs. She refused to continue the treatment when chest CT showed that the tumor was shrunk to 4.2x5.8cm, left pneumonia and pleural effusion disappeared. Her weight did not decline with KPS 100 and pain score 0.

The patient came to our department the third time complaining of increasing paining of chest, with tumor marker increased obviously on 1st Dec. 2010. She received another four cycles of weekly low dose pemetrexed till 1st Feb. 2011 when her symptom alleviated with KPS 100 and pain score 0. Radiation therapy had been taken from 25th Apr. to 12th May 2011 and the tumor reduced from 9x6cm to 8x5cm simultaneously.

She received Gamma Knife radiosurgery when cerebral CT showed a metastatic tumor (3.1x3.1cm) in right temporal lobe on Feb. 8th 2012. Chest CT showed multiple metastasis of double lung (maximum size is 1.5 cm) on Mar. 23th 2012, after four cycles of pemetrexed and bevacizumab (pemetrexed 200 mg qw, bevacizumab 5mg/kg q2w) therapy, she reached partial remission. NVB was used for maintenance therapy from Aug. 2th 2012 to Apr. 2013 because she cannot afford bevacizumab anymore. Gamma Knife of head was operated in Jun. 2013 again for the brain MRI showed more metastasis than before. Meanwhile the tumor marker was much higher than before, she accepted another 4cycles weekly low dose pemetrexed till Jun. 2014 discontinuously. Tumor marker declined again during this time while she was in good condition. She died of cardiac failure on Jan. 6th 2015. The change of tumor markers in serum and left apical lung nodule during therapy can be seen in (Figure 1,2).

Discussion

NSCLC accounts for approximately 80-85% of all lung cancer cases [11,12]. About 50% of the patients present advanced disease at the time of diagnosis and 5-year survival rate is less than 5% [13].

Pemetrexed is a novel folate analogue [14,15]. During blocking the folate-requiring enzymes such as dihydrofolate reductase, thymidylate synthase (TS) and glycinamide ribonucleotide formyltransferase, it can also inhibit the de novo synthesis of thymidine and purine nucleotides.

Pemetrexed have been approved in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma who have unresectable nidus or no otherwise candidates for curative therapy by North American and European regulatory agencies [16], and as the single agent for the therapy of locally advanced or metastatic NSCLC patients.

Conventional chemotherapy of pemetrexed was 500 mg/m^2, q^3w [17]. Elderly advanced NSCLC patients, especially those who have failed to the frist-line chemotherapy and targeted drugs, can hardly receive such remedy. There is no criteria treatment protocols for these patients during that time especially when they are resistant to EGFR-TKIs. This case shows weekly low dose pemetrexed therapy (130-150

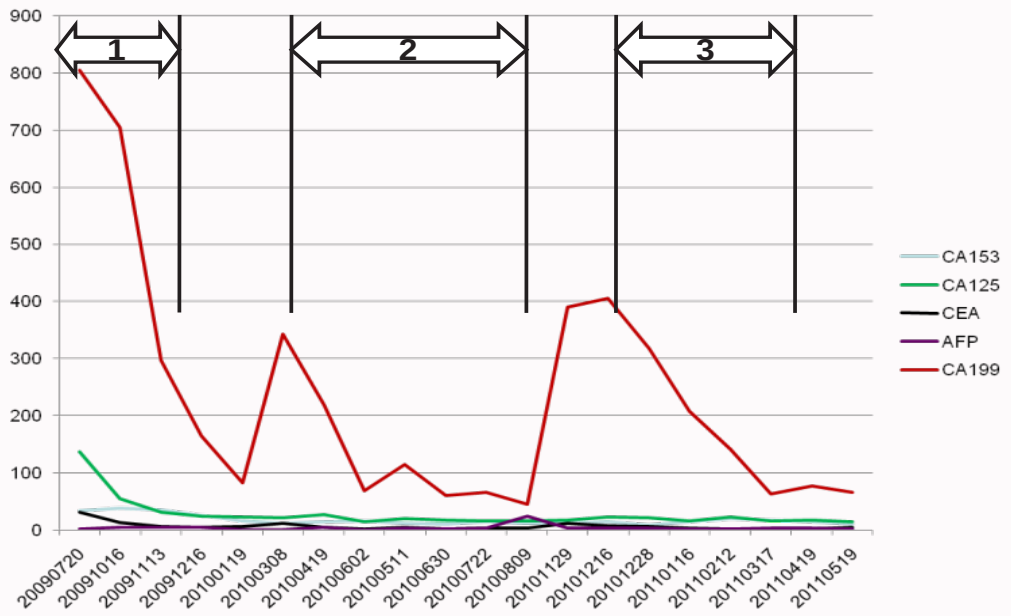

Figure 2: The change of tumor markers in serum during therapy.

mg/m^2, qw, q28d) is effective. Phase I clinical trials of pemetrexed (500mg/m^2, q3w, without folic acid and vitamin B_{12}) was terminated due to toxic side effects. Our new therapy is effective which might be determined by low dose and toxicity.

The patient could reach partial remission each time she received new therapy although she had failed to first line chemotherapy and EGFR-TKI. It suggests that the tumor might recur nearly 100 days later after the former chemotherapy ended without drug resistance if we adopt the same plan again within six months of last chemotherapy.

In general, hematological and non-hematological toxicities of pemetrexed can be reduced through routine supplementation [18]. In this case, toxicities are acceptable. Patients adopts treatment weekly can enhance their obedience since they can receive this therapy at outpatient service. Weekly low dose pemetrexed might be suitable for elderly advanced lung adenocarcinoma patients even when they had used pemetrexed before.

To our best knowledge, this is the first effective therapy of weekly low dose pemetrexed which has been gradually proved and demonstrated by nearly twenty cases in our department. The related mechanism investigation is under way through clinical trials and subsequent laboratory analysis.

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