Case Report

Effectiveness of pemetrexed-based chemotherapy and radiation therapy in RET-rearranged lung adenocarcinoma: a mono-institutional case series

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Abstract: Rearranged during Transfection gene (RET) fusions occur in 0.7–2% of non-small cell lung cancer (NSCLC) representing a novel target for oncogene addicted disease. Retrospective analyses showed remarkable response to the chemotherapic anti-folate drug Pemetrexed in patients affected by RET-fusion NSCLC, while immunotherapy does not assure remarkable efficacy. Nowadays, novel therapies are enriching the number of specific anti-RET strategies. The present mono-institutional case series reports significant responses to Pemetrexed, and radiation therapies performed on previously identified or oligo-progressing metastatic sites. Next Generation Sequencing conducted on histological tissue in two cases and on blood specimen in one case detected RET fusion in the clinical course after chemotherapy. As other oncogene addicted subtypes of NSCLC, such as EGFR mutated, ALK and ROS1 rearranged, radiation treatment of residual or oligo-progressing lesions appeared to prolong the clinical benefit from oncological treatments. Despite specific anti-RET treatments are under evaluation for RET-positive non squamous NSCLC, Pemetrexed assured optimal and durable clinical response. The addition of loco-regional treatment of residual or oligo-progressive disease prolonged the time to chemotherapy failure. The present manuscript aims at arising the hypothesis that loco-regional treatment could be considered for oligo-metastatic disease with consolidation extent and could allow beyond progression Pemetrexed-based therapy for oligo-progressive disease.

Keywords: Rearranged during Transfection gene (RET)-fusion; lung adenocarcinoma; pemetrexed; radiation therapy

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Introduction

Novel discoveries are enriching genomic landscape of non-small cell lung cancer (NSCLC). Clinicians should investigate mutational status of EGFR, BRAF, ALK and ROS1 and histochemical expression of programmed death-ligand 1 (PD-L1) before starting fist line treatment for unresectable or metastatic disease. Rearranged during Transfection gene (RET) fusions represent a novel but rare oncogenic driver; ongoing trials are evaluating efficacy of single or combined anti-RET treatments for RET rearranged disease. The tyrosine kinase inhibitor (TKI) pralsetinib showed consistent objective response rate and disease control rate in naïve and platinum treated patients leading to FDA drug approval for RET-rearranged NSCLC (1).

RET binds the glial cell–derived neurotrophic factors and is involved in cell proliferation and migration (2). Somatic fusions CCDC6-RET (PTC1) (3) and NCOA4-polymerase chain reaction RET (PTC3) (4) are genomic determinants of radiation-induced and sporadic papillary thyroid cancer.

KIF5B-RET, CCDC6-RET, and NCOA4-RET are the most common RET fusions in the context of lung cancer. They cause a RET dimerization paving the way to its hyperactivation. Mitogen-activated protein kinase (MAPK), PI3K/AKT and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways are the downstream mediators causing uncontrolled cell proliferation (5,6).

Fluorescence in situ hybridization (FISH) and reverse transcriptase (PCR) show far higher sensitivity than immunochemistry (IHC) in detecting RET fusions.

RET rearrangements are more frequent in non-smoker patients diagnosed with lung adenocarcinoma at young age and guarantee good clinical response to Pemetrexed. Indeed, RET fusion positive NSCLC is associated with smaller primitive lesions, more frequent N2 nodal involvement, poorer differentiation, solid-like histology, and signet cell phenotype (7).

The present case series aims at describing features and outcomes of RET-rearranged NSCLC treated with Pemetrexed and concomitant radiation therapy at our center. Three patients showed significant and prolonged time to treatment failure; two patients discontinued Pemetrexed cause of drug induced unacceptable toxicities and stereotaxic radiation treatments allowed to prolong time to treatment failure during follow up.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/pcm-21-1).

Cases presentation

Case 1

A 55 years old male Caucasian patient was diagnosed with lung adenocarcinoma of right medium lobe with mediastinal nodal and single seventh right rib metastases in July 2018. PD-L1 IHC expression was 0%, EGFR did not harbor any mutation, ALK and ROS1 were not rearranged. pTNM stadium was pT4N2M1 according to the eight edition of the International Association for the Study of Lung Cancer (IASLC). The patient, previous light smoker (7–8 cigarettes per day until 30 years old), started first line chemotherapy with Cisplatin plus Pemetrexed in August 2018. Shift from Cisplatin to Carboplatin since the second administration was necessary cause of ototoxicity. The first PET CT scan performed in November 2018 showed ubiquitous partial metabolic and dimensional response thus the patient started maintenance therapy with Pemetrexed. Consolidation concomitant stereotactic radiation therapy on nodal metastases and lung primary cancer was carried out in December 2018 for a total dose of 46 Gray (Gy; 200 cGy per day) and 66 Gy (200 cGy/day), respectively. The CT scan of March 2019 reported further response. The patient received consolidative stereotactic radiation therapy on the rib metastasis in May 2019. Subsequent PET CT scans showed complete metabolic response of disease and morphologic reduction of the bone lesion. In accordance with the patient, we decided to discontinue Pemetrexed on July 2019 cause of cumulative toxicity, in particular disabling fluid retention, skin toxicity and progressive hypercreatininemia. The PET CT scan of November 20 confirmed complete metabolic response and the patients is currently continuing follow up. Next Generation Sequencing of pulmonary biopsy revealed in May 2020 the presence of RET-KIF5B fusion, providing a biological rationale for prolonged response to Pemetrexed in a young light smoker patient diagnosed with metastatic lung adenocarcinoma. Stereotaxic treatments might have strengthened response to Pemetrexed-based chemotherapy.

Case 2

A 54 years old Caucasian woman received left superior lobectomy for lung adenocarcinoma in March 2015. Due to pathological status pT1bN2 according to the seventh edition of IASLC, adjuvant chemotherapy with four cycles of Cisplatin plus Gemcitabine and subsequent radiotherapy were scheduled. The PET CT scan performed in December 2017 showed left axillary, multiple vertebral and left pulmonary relapse. PD-L1 IHC was 10%, EGFR, ALK and ROS1 were wild type. The patient started chemotherapy with Carboplatin and Pemetrexed in February 2018, but discontinued maintenance with Pemetrexed in July 2018 cause of hypercreatininemia. Radiation therapy treated mediastinal nodal (50 Gy, 25 cGy per day) in December 2018 and the sixth and seventh cervical vertebrae (24 Gy, in two fractions) with antalgic extent in February 2019. The patient continued follow up until September 2019 when CT scan revealed bone progressive disease and the patient began second line treatment immunotherapy with Atezolizumab. NGS on liquid biopsy of June 2020 revealed RET-KIF5B fusion. The patient's disease showed significant sensitivity to Pemetrexed, but such a long-lasting time to treatment

failure during follow up could have been positively influenced by radiation treatments. The patient is currently receiving anti-RET therapy with Pralsetinib in fourth line setting since August 2020 and first radiological restaging of October showed partial mediastinal response.

Case 3

A 63 years old Caucasian woman addressed to out center cause of diagnosis of PD-L1 negative, ROS1 and ALK not rearranged lung adenocarcinoma with diffuse axial skeletal secondary lesions. Prior liquid biopsy and subsequent bone biopsy did not report any EGFR mutation. The patient started first line chemotherapy with Cisplatin plus Pemetrexed in November 2019. The first reassessing CT scan of February 2020 showed partial pulmonary response of disease, and stable disease was reported on May 2020. The bone scintigraphy of September 2020, compared with previous exam of August 2019, showed increased metabolic skeletal disease. Despite the 3 months distance between initial scintigraphy and chemotherapy starting, we assessed the disease cause of increase of bone pain. Since Next Generation Sequencing (NGS) of metastatic tissue revealed RET-NCO4 fusion in January 2020, the patient started second line with Pralsetinib in December after antalgic radiation therapy of total 30 Gy (300 cGy per day) having experienced an almost 12 months progression free survival (PFS).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

Discussion

First analyses of RET fusions influence upon oncologic treatment rely on retrospective studies evaluating chemo-sensitivity of oncogene addicted lung cancer and their prevalence in NSCLC varies between 0.7% and 2% (7-11).

As other oncogene addicted NSCLC, brain involvement in RET-positive patients is present at the diagnosis in 25% of cases, but cumulative lifetime incidence reaches 46% (12).

Pemetrexed is an antifolate chemotherapic agent active on folate-dependent enzymes, such as thymidylate synthase (TS), glycinamide ribonucleotide formyl transferase, and dihydrofolate reductase.

In a cohort of Asian 68 patients affected by adenocarcinoma, Platinum plus Pemetrexed assured better median (PFS) in 4 RET-fusion positive patients in comparison with RET-negative patients (7.5 *vs.* 5 months) without a significant difference in OS. Lower TS expression in RET-positive subgroup accounted for better response to anti-folate chemotherapy (13).

Pemetrexed based chemotherapy showed higher responses in Asian RET-positive patients versus other regimens, such as Platinum plus Paclitaxel, and Platinum plus Gemcitabine, both in first (PFS 9.2 *vs.* 5.2 months) and second line setting (4.9 *vs.* 2.8 months) (14).

In a Korean retrospective cohort, Cisplatin or Carboplatin plus Pemetrexed, administered in first- or second line setting in 46 patients, guaranteed objective response rate (ORR) of 63% and disease control rate (DCR) of 91.3%. Median PFS and OS were respectively 9 and 24.1 months (15).

A global registry found out that 66 RET-positive patients treated with first line combination of Platinum plus Pemetrexed experienced a median PFS of 6.4 months and median OS was 23.6 months (16).

ROS-1 and ALK-rearranged NSCLC show sensitivity to Pemetrexed (17), and a large American mono-institutional study pointed out similar response upon Pemetrexed in RET-positive lung adenocarcinoma. Median PFS, Time to Progression (TTO) and Median Time to Treatment Discontinuation were respectively 19, 20 and 21 months. ORR was 45% (18).

RET-positive adenocarcinomas usually display low Tumor Mutational Burden (TMB) and PD-L1 IHC expression (14), not by chance response to immunotherapy is poor, with a median PFS between 2.1 (19) and 3.4 months (20). ORR and DCR were respectively 7.7% and 46.2% in the mentioned Korean retrospective cohort (15). Similar ORR of 6% was reported in the global IMMUNOTARGET registry that evaluated the outcomes of 16 patients treated with Immunotherapy in second or third line (21).

Specific TKIs-based treatments represent the standard treatment for oncogene addicted NSCLC.

Despite the significant and persistent response to TKIs, oligo-progressive EGFR (22,23) and ALK (24) positive NSCLC can benefit from beyond progression strategies and loco-regional treatments are often offered extending the time to treatment failure and the overall survival.

In addition, consolidative radiation treatment is associated with improved clinical outcomes in patients affected by oligometastatic oncogene addicted NSCLC (25).

In our small mono-institutional case series, despite the patients did not receive RET-specific treatments,

Pemetrexed-based chemotherapy assured optimal responses as expected. Comparably to other oncogene addicted lung diseases, loco-regional approaches guaranteed prolonged time to treatment failure, even in patients that discontinued chemotherapy cause of unacceptable toxicity.

Novel anti-RET strategies are being evaluated but Pemetrexed confirmed its high activity against RET-positive disease. We hypothesize that locoregional radiation therapy may represent a reasonable option for patients with oligo-metastatic or oligo-progressive metastatic RET lung adenocarcinoma that discontinue Pemetrexed.

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