Partial Response to Platinum Doublets in Refractory EGFR-Positive Non-Small Cell Lung Cancer Patients after RRx-001: Evidence of Episensitization

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Key Words

Partial response · Platinum doublets · Refractory EGFR · Non-small cell lung cancer · RRx-001

Abstract

RRx-001, an experimental systemically non-toxic epi-immunotherapeutic agent, which potentiates the resensitization of resistant cancer cells to formerly effective therapies, is under active investigation in several clinical trials that are based on sequential or concomitant rechallenge to resistant first- or second-line regimens. One of these trials is designated TRIPLE THREAT (NCT02489903), because it explores the conditioning or priming effect of RRx-001 on three tumor types – non-small cell lung cancer (NSCLC), small cell lung cancer and high-grade neuroendocrine tumors – prior to re-administration of platinum doublets. In follow-up to a recent case study, which describes early monotherapeutic benefit with RRx-001 in a refractory EGFR-mutated NSCLC tumor, we present subsequent evidence of a radiological partial response to reintroduced platinum doublets after RRx-001. For the 50% of patients with EGFR-mutated NSCLC who progress on EGFR-tyrosine kinase inhibitors (without evidence of a T790M mutations) as well as platinum doublets and pemetrexed/taxane, no other clinically established treatment options exist. A retreatment of these therapies in EGFR-positive NSCLC pa-

tients via priming with epigenetic agents such as RRx-001 constitutes a strategy to ‘episenitize’ tumors (i.e. reverse resistance by epigenetic means) and to extend overall survival.

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Introduction

Therapy selection guidelines for EGFR-mutated non-small cell lung cancer (NSCLC) patients are as follows:

- First line: tyrosine kinase inhibitors (TKIs) for EGFR-sensitizing mutations (exons 18,19, and 21), including erlotinib [1] and afatinib [2], approved for use in the United States, as well as gefitinib [3], which has recently received reapproval for use in the United States.
- Second-line TKIs: upon progression, it is recommended to biopsy the site of progression to determine if a new resistant mutation has developed (exon 20 mutation) T790M. If this new resistant mutation exists, patients are now offered osimertinib [4], which has recently been approved in the United States.
- Second line if the patient has no T790M mutation: 4–6 cycles of platinum-based chemotherapy such as platinum/pemetrexed [5], after which patients are observed for evidence of disease progression [6]. Third-line therapy generally follows progression. Elderly patients with significant comorbidities appear to tolerate the platinum doublets, carboplatin and nanoparticle albumin-bound paclitaxel with a reduced toxicity profile as an option [7].
- Third line: single agent docetaxel or pemetrexed (whichever has not been used so far). After disease progression, in the absence of clinical deterioration, patients may be referred for clinical trials (fig. 1).

While the successful reintroduction to TKIs or standard chemotherapy after progression in EGFR-mutated NSCLC patients has been documented in the literature [8], a rechallenge strategy is generally contraindicated on the assumption that re-exposure will yield toxicity rather than benefit due to the stability of the chemo-resistant phenotype [9, 10]. An emerging paradigm called episenitization, which attempts to epigenetically condition or ‘prime’ the tumor to re-respond to refractory chemotherapy, challenges the long-held practice of permanently discontinuing a particular treatment at the time of disease progression [11]. Hypothetically, like a therapeutic ‘do-over’, episenitized patients restart prior effective regimens each time from a state of scratch rather than from the disadvantage of a progressively entrenched non-responsiveness, potentially leading to the ‘chronification’ of a once fatal disease. Accordingly, in a phase II clinical trial called TRIPLE THREAT (NCT02489903), patients with three tumor types – NSCLC, small cell lung cancer and high-grade neuroendocrine tumors or carcinomas (hence the name TRIPLE THREAT) – receive the experimental systemically non-toxic immuno-epigenetic agent, RRx-001 [12–14], until RECIST v. 1.1-defined progression, followed by the reintroduction of platinum doublets. Figure 2 shows a schematic description of the TRIPLE THREAT trial.

In the present report, a follow-up to a recently published case report in this journal [15], which details dramatic RRx-001-induced intratumoral necrosis and immune infiltration in an EGFR-mutated NSCLC patient, evidence of subsequent episenitization to platinum doublets in the form of a partial response is described.

Case

A 49-year-old never-smoking male with EGFR-sensitizing positive mutated NSCLC and clear failure to erlotinib as well as carboplatin and pemetrexed received 5 weekly doses of intravenous RRx-001 (4 mg) with simultaneous infusions of autologous blood per the TRIPLE THREAT (NCT02489903) protocol. In the 5th week of treatment, he was reimaged with PET/CT due to progressively worsening abdominal pain, which demonstrated a dramatically enlarged necrotic mass with a thin capsule of apparently viable tumor (fig. 3).

Despite this clearly beneficial response to treatment, tumor enlargement mandated discontinuation of RRx-001 per RECIST v.1.1 criteria for progression, and the patient was restarted on platinum doublets (cisplatin 75 mg/m² i.v. + nab-paclitaxel 100 mg/m² i.v.). After only one cycle, the patient, coping poorly with the persistent abdominal pain, nausea, cachexia, and fatigue, due to the size of the mass, requested an extended break from treatment to spend time with his wife and small children. Almost 3 weeks later, the investigators were pleasantly surprised when the patient called to report that his energy, appetite, productivity, and weight had recovered in the absence of treatment to the point that for the first time in recent memory he was looking forward to the holidays.

On December 22, 2015, the patient was reimaged with PET/CT, which demonstrated a partial response (30% decrease in sum from baseline) as well as a metabolic response relative to the previous PET/CT on November 27, 2015. These images are shown (fig. 3).

Discussion

This follow-up case report documents an unprecedented clinical and radiological partial response of a patient with platinum and TKI-refractory EGFR-mutated NSCLC with no further treatment options, having progressed through multiple lines of targeted and systemic chemotherapy, including a previous clinical trial with TH-4000 (tarloxotinib), a pro-drug of a TKI [16], which did not benefit the patient. His response was all the more remarkable because it occurred after only one dose of protocol-mandated rechallenge with platinum doublets, demonstrating a potential epigenetic resensitization i.e. 'episensitization' due to RRx-001 pretreatment or priming.

Patients with platinum and TKI-refractory EGFR-mutated NSCLC have an average survival measured in months only [17]. Moreover, from the moment that treatment starts in first line, the clock is winding down along with viable therapeutic options, and it is only a question of time when – rather than if – resistance and treatment failure will occur. Since the accumulation of treatment-induced epigenetic changes are in theory reversible [18], unlike genetic mutations, the episensitization tabula rasa has the potential to wipe the resistance slate clean and rewind the ticking doomsday clock all the way back to first or second line. The result, hopefully, is improved functional status and overall survival, translating to more quality time, which is what occurred in the case of this fortunate patient.

Statement of Ethics

The case report was conducted according to the Declaration of Helsinki principles. The patient gave written informed consent.

Disclosure Statement

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Fig. 1. NSCLC EGFR mutation-positive treatment algorithm.

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Fig. 2. Schema of the TRIPLE THREAT clinical trial. SCLC = Small cell lung cancer; HGNEC = high-grade neuroendocrine carcinoma; PD = progressive disease; SD = stable disease.

Fig. 3. On the left, PET/CT from November 27, 2015 demonstrating RRx-001-induced central infarction of an abdominal metastasis. On the right, PET/CT from December 22, 2015 showing dramatic shrinkage of the lesion after one dose of cisplatin and pemetrexed, indicative of episensitization. The high FDG uptake in the discontinuous rind of the tumor may be secondary to invasion by inflammatory cells. Note the FDG-avid myocardium just above the tumor on the left.