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RRx-001 in Refractory Small-Cell Lung Carcinoma: A Case Report of a Partial Response after a Third Reintroduction of Platinum Doublets

Corey A. Carter[a] Bryan T. Oronsky[b] Scott Z. Caroen[b] Jan J. Scicinski[b] Aiste Degesys[a] Michelle M. Kim[c] Arnold L. Oronsky[d] Harry Lybeck[h] Pedro Cabrales[e] Neil Oronsky[f] Tony Reid[g] Joseph Roswarski[a] Christina Brzezniak[a]

[a]Walter Reed National Military Medical Center, Murtha Cancer Center, Bethesda, Md., [b]EpicentRx Inc., Mountain View, Calif., [c]Department of Radiation Oncology, University of Michigan, Ann Arbor, Mich., [d]InterWest Partners, Menlo Park, Calif., [e]Department of Bioengineering, University of California San Diego, La Jolla, Calif, [f]CFLS Data, Mountain View, Calif., and [g]Moores Cancer Center, University of California San Diego, La Jolla, Calif., USA; [h]Department of Physiology, University of Helsinki, Helsinki, Finland

Key Words
Small-cell lung cancer · Resistance · Platinum doublets · Epigenetic · Resensitization · Episensitization

Abstract
RRx-001 is a pan-active, systemically nontoxic epigenetic inhibitor under investigation in advanced non-small cell lung cancer, small-cell lung cancer and high-grade neuroendocrine tumors in a Phase II clinical trial entitled TRIPLE THREAT (NCT02489903), which reexposes patients to previously effective but refractory platinum doublets after treatment with RRx-001. The purpose of this case study is first to report a partial response to carboplatin and etoposide in a patient with small-cell lung cancer pretreated with RRx-001, indicating episensitization or resensitization by epigenetic mechanisms, and second to discuss the literature related to small-cell lung cancer and episensitization.

Dr. Corey A. Carter
Walter Reed National Military Medical Center
8901 Wisconsin Ave, Bethesda, MD 20889 (USA)
E-Mail coreycartermd@gmail.com

Introduction

Small-cell lung cancer (SCLC), which comprises approximately 10–15% of all lung cancers [1], is a neuroendocrine tumor, previously known as oat cell carcinoma, that is closely linked with tobacco smoking [2] and characterized by an aggressive and rapid pattern of metastases, limited treatment options following progression, and overall poor prognosis [3]. The disease is traditionally divided into two stages: limited-stage disease (LD), confined to one hemithorax encompassable in a single radiation port, and extensive-stage disease (ED), extending beyond those boundaries [4], which comprise the vast majority of patients at initial diagnosis [5, 6]. For extensive-disease SCLC, the standard first-line regimen is etoposide-platinum (EP) doublets followed by topotecan, approved for second-line treatment, since progression is the rule after first-line EP despite the fact that SCLC is initially chemosensitive (with response rates to first-line treatment on the order of 70–90% in LS disease and 50–60% in ED disease [7]). In ED, despite a response rate of 15–28% [8] to topotecan [9], the median OS rarely exceeds 6 months. According to the current nomenclature [10], SCLC is categorized as 'sensitive relapsed' (PFS >3 months), 'resistant' (PFS <3 months) and 'refractory' (progression through first-line treatment). In general, subsequent readministration of EP doublets is contraindicated in resistant and refractory disease due to the likelihood of undue toxicities (myelosuppression and nephrotoxicity, for example) without benefit, since therapeutic resistance in these contexts is, with exceptions, construed as a stable and immutable trait [11]. No guidelines are available about platinum doublet rechallenge after initial and secondary failures.

Pretreatment or priming with epigenetic inhibitors, like the approved DNA demethylators, e.g., 5-azacitidine (azacitidine, AZA) and 2′-deoxy-5-azacitidine (decitabine, DAC) and the histone deacetylases, e.g., vorinostat and romidepsin as well as experimental RRx-001, has been identified as a nascent strategy, still in its infancy, to attenuate or reverse resistance to chemotherapy and immunotherapy [12–14], particularly in non-small cell and ovarian cancers. The term 'episensitization [15]' has been coined for this priming paradigm. RRx-001, in particular, has demonstrated evidence of episensitization to refractory irinotecan in the context of a Phase II clinical trial entitled ROCKET in metastatic colorectal cancer [16–18].

TRIPLE THREAT (NCT02489903) is an ongoing open-label Phase II trial in non-small lung cancer, SCLC and high-grade neuroendocrine tumors, which investigates a resensitization strategy to previously administered, but now refractory, platinum doublets following treatment with and progression on (by RECIST vs. 1.1 criteria) single agent RRx-001 mixed ex vivo with 100 ml of autologous blood prior to infusion. The rationale for this unusual method of administration is related to the red blood cell partitioning of RRx-001, which binds with high affinity to a cysteine residue in the β-chain of Hb (Cys β93), displacing nitric oxide (NO) in the process. When NO is displaced in vivo via standard intravenous infusion, it stimulates venous nociceptors, with a mild to moderate sensation of pain or discomfort for patients; however, in the infusion bag, mixed with blood, the NO is reabsorbed by the red blood cells, which appears to completely abrogate the hyperalgesia, resulting in a well-tolerated and rapid (~30 min) infusion.

Herein, we report a case of a patient with extensive refractory ED-SCLC who was 'episensitized' to cisplatin and etoposide, with a partial response, after treatment with weekly intravenous RRx-001 autologous blood mix.

Case Report

Patient 001–001, a 49-year-old male veteran, former smoker, with a diagnosis of extensive-stage SCLC, completed six cycles of carboplatin and etoposide in December 2012. Having progressed approximately 6 months later with 'sensitive relapsed' (PFS >3 months) disease, he was enrolled on a clinical trial at the NIH in July 2013 where he received six cycles of cisplatin and etoposide followed by maintenance with the HDAC inhibitor belinostat. Approximately 1 year after completion of the NIH trial, with symptoms of fatigue and inappetence due to disease progression as well as dyspnea and decreased exercise tolerance from a large unilateral pleural effusion, he enrolled as the first patient (001–001) on the TRIPLE THREAT clinical trial at Walter Reed in June 2015. After the first dose of RRx-001, and continuing for the next 8–9 weeks, the patient reported a significantly increased appetite for and consumption of fried foods, specifically pork chops, and desserts, which led to dyspeptic symptoms. His fatigue, shortness of breath and exercise tolerance also significantly improved to the point that he resumed uphill running and lifting weights. A CT scan at 6 weeks (fig. 1), correlating with the symptomatic improvement, demonstrated near complete resolution of the unilateral malignant pleural effusion. In addition, his target lesions shrank by 7% (not shown).

Unfortunately, nearly 10 weeks after the start of TRIPLE THREAT, patient 001–001 developed 'travelers thrombosis' and pulmonary embolism presumably from a prolonged (10 h) car ride, which prompted the PI to discontinue RRx-001 on suspicion of symptomatic progression since the patient began to complain of fatigue and inappetence as well as dyspnea associated to pulmonary embolism, even though repeat CT scans did not confirm radiologic progression. At this point, per protocol, since the patient still met all inclusion/exclusion criteria, he was rechallenged for a third time with EP doublets and, despite expected toxicities of fatigue and anorexia, he reported improved performance status. At 6 weeks after reintroduction of therapy, repeat CT scans demonstrated a partial response with an approximate 32% decrease in tumor size (fig. 2). One month later, a confirmatory scan showed a 50% decrease in tumor size, indicative of continued cytotoxic activity.

Discussion

To the best of our knowledge, TRIPLE THREAT is the first and only clinical trial to investigate resensitization or episensitization, since RRx-001 is an epigenetic inhibitor [19] in SCLC as well as NSCLC and neuroendocrine tumors. As a highly aggressive tumor with a uniformly dismal prognosis and an unmet need for effective therapeutic options, SCLC is extremely difficult to treat: the median survival time following recurrence rarely exceeds 6 months, the 2-year survival is <10%, and there are virtually no 5-year survivors [20], requiring innovative strategies to address the difficult challenge of salvage treatment of relapsed SCLC.

DNA methyltransferase and HDAC inhibitors have demonstrated the potential to reverse therapeutic resistance [21] in multiple tumor types because epigenetic alterations, an important driver of carcinogenesis and progression, are, in theory, reversible. Paradoxically, these alterations are also stably maintained through mitotic cell division, leading to a kind of epigenetic memory [22], with priming of responses to temporally separate and subsequent, rather than simultaneous, therapy since the induced pattern of gene transcription persists.

The clinical course of this SCLC patient (001–001) suggests, with the usual caveats about making generalizations from 'n-of-1' results, that reintroduction of etoposide-platinum after

initial treatment with RRx-001, leading to episensitization, is a safe and effective strategy for solid tumor types previously treated with platinum doublet-based chemotherapy. The Phase II TRIPLE THREAT clinical trial is ongoing, having enrolled 5 patients to date, none of whom, besides patient 001–001, have progressed on RRx-001, and their data will also be reported, if episensitization, anticipated here as elsewhere, is demonstrated.

Statement of Ethics

The research behind this case report complies with the guidelines for human studies. Any subjects have given their informed consent in the study and the study protocol has been approved by the relevant institute's institutional review board, also known as an independent ethics committee, ethical review board, or research ethics board.

Disclosure Statement

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References

1 Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL, Piccirillo J: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539–4544.
2 van Meerbeeck JP, Fennell DA, De Ruysscher DK: Small-cell lung cancer. Lancet 2011;378:1741–1755.
3 Byers LA, Rudin CM: Small cell lung cancer: where do we go from here? Cancer 2015;121:664–672.
4 Kamel D, Boag A, Bezjak A, Mates M: Prolonged progression free interval in a patient with locally recurrent small cell lung cancer presenting with cerebellar paraneoplastic syndrome. Can Treat Commun 2015, DOI: 10.1016/j.ctrc.2015.08.005.
5 Clark R, Ihde DC: Small-cell lung cancer: treatment progress and prospects. Oncology (Williston Park) 1998;12:647–658; discussion 661–663.
6 Hagmann R, Hess V, Zippelius A, Rothschild SI: Second-Line Therapy of Small-Cell Lung Cancer: Topotecan Compared to a Combination Treatment with Adriamycin, Cyclophosphamide And Vincristine (ACO) – a Single Center Experience. J Cancer 2015;6:1148–1154.
7 Hurwitz JL, McCoya F, Scullin P, Fennell DA: New Advances in the Second-Line Treatment of Small Cell Lung Cancer. Oncologist 2009;14:986–994.
8 Owonikoko TK, Behera M, Chen Z, Bhimani C, Curran WJ, Khuri FR, et al: A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol 2012;7:866–872.
9 Spira A, Ettinger DS: Extensive-stage small-cell lung cancer. Semin Surg Oncol 2003;21:164–175.
10 Glisson BS: Recurrent small cell lung cancer: update. Semin Oncol 2003;30:72–78.
11 Oronsky BT, Oronsky AL, Lybeck M, Oronsky NC, Scicinski JJ, Carter C, Day RM, Rodriguez Orengo JF, Rodriguez-Torres M, Fanger GF, Reid TR: Episensitization, defying time's arrow. Front Oncol 2015;5:134.
12 Oronsky B, Oronsky N, Knox S, Fanger GR, Scicinski J: Episensitization: therapeutic tumor resensitization by epigenetic agents: a review and reassessment. Anticancer Agents Med Chem 2014;14:1187–1198.
13 Liu SV, Fabbri M, Gitlitz BJ, Laird-Offringa I: Epigenetic rherapy in lung cancer. Front Oncol 2013;3:135.
14 Carter C, Reid T, Fisher G, Cho-Phan C, Kunz P, Kaiser H, Oronsky B, Fanger G, Caroen S, Parker C, Scicinski J: Early results from a phase 2 study of RRx-001, a novel, triple epigenetic inhibitor, showing resensitization to irinotecan in colorectal cancer, AACR 2015 Abstract Control Number: 8836. Ann Oncol 2015;26:ii4–ii5.
15 Strauss J, Figg WD: Epigenetic approaches to overcoming chemotherapy resistance. Lancet Oncol 2015;16:1013–1015.
16 Reid T, Oronsky B, Scicinski J, Scribner C, Knox S, Ning S, Peehl D, Korn R, Stirn M, Fanger G, Carter C, Oronsky A, Taylor M, Fitch W, Cabrales P, Burris HA, Kim M, Lao C, Infante J: A Phase I, first-in-human, trial

of RRx-001, a novel oxidative epigenetic agent, in patients with advanced cancer. Lancet Oncol 2015;16:1133–1142.
17 Carter C, Reid T, Fisher G, Cho-Phan C, Kunz P, Kaiser H, Oronsky B, Fanger G, Caroen S, Parker C, Scicinski J: Early Results: 'ROCKET' a phase II Study of RRx-001, a novel triple epigenetic inhibitor, Resensitization to Irinotecan in Colorectal Cancer. 13th International Congress on Targeted Anticancer Therapies: TAT 2015. Paris, Mar 2–4, 2015.
18 Oronsky BT, Oronsky AL, Lybeck M, Oronsky NC, Scicinski JJ, Carter C, Fanger GR, Reid TR: Episensitization: a new word for a new concept; in Egger G, Arimondo P (eds): Drug Discovery in Cancer Epigenetics. Oxford, Elsevier, 2016, pp 407–436.
19 Scicinski J, Fisher G, Carter C, Cho-Phan C, Kunz P, Ning S, Knox S, Oronsky B, Caroen S, Parker C, Fanger G, Reid T: The development of RRx-001, a novel nitric-oxide-mediated epigenetically active anticancer agent, Invited Presentation at 4th International Workshop on Nitric Oxide in Cancer Therapy, Seville, Mar 13–14, 2015.
20 Okuno SH, Jett JR: Small cell lung cancer: current therapy and promising new regimens. Oncologist 2002;7:234–238.
21 Brown R, Curry E, Magnani L, Wilhelm-Benartzi CS, Borley J: Poised epigenetic states and acquired drug resistance in cancer. Nat Rev Cancer 2014;14:747–753.
22 Jaenisch R, Bird A: Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nature Genetics 2003;33:245–254.

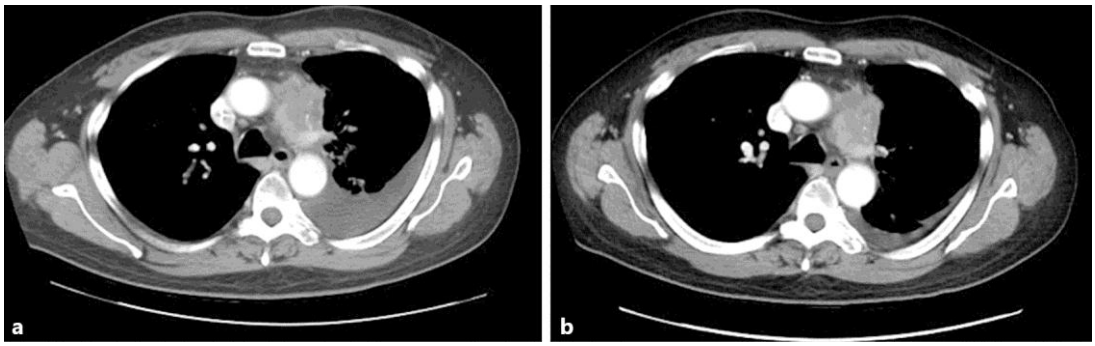

Fig. 1. CT scans before and after treatment demonstrating a left-sided pleural effusion (**a**) before treatment with RRx-001 and (**b**) its near complete resolution after 6 weeks.

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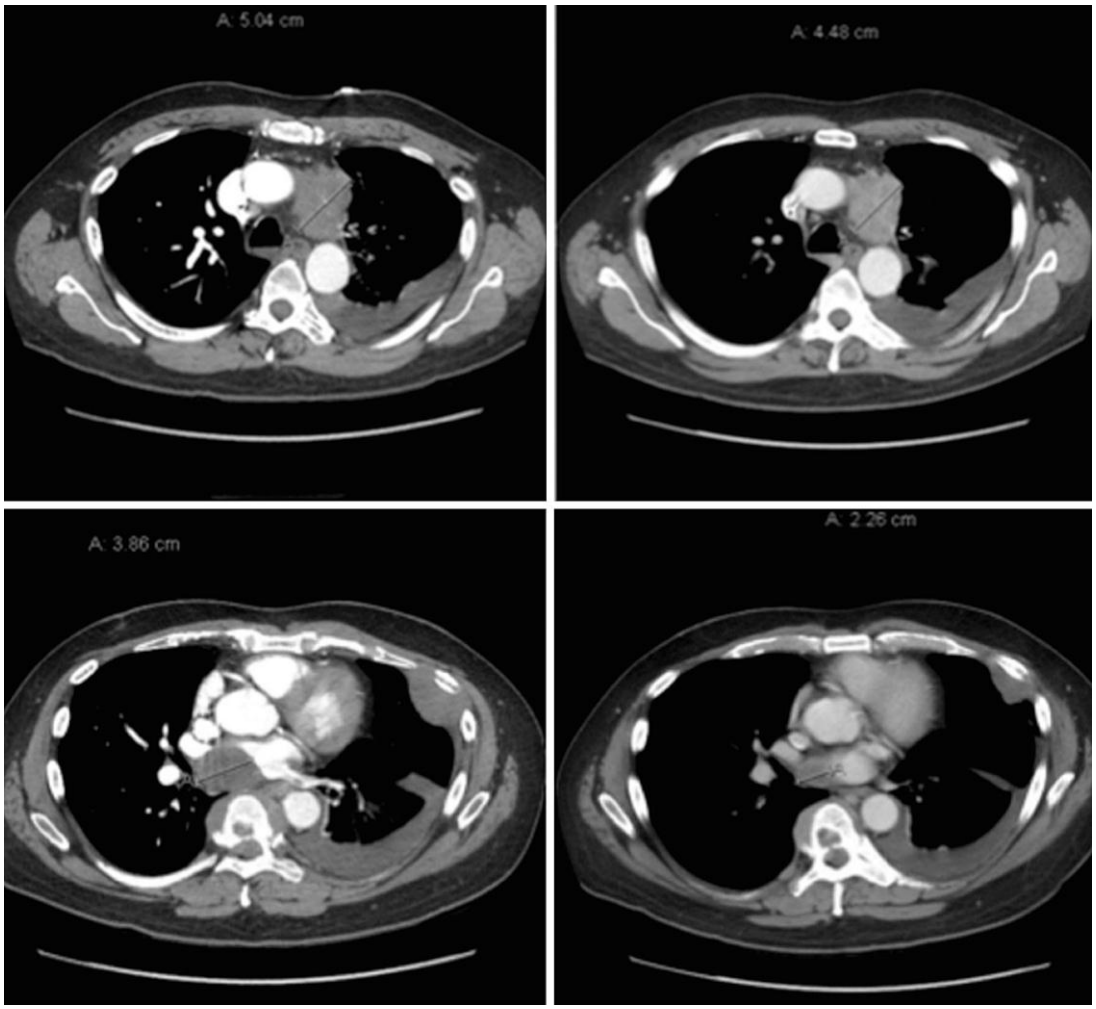

Fig. 2. CT scans of the lungs demonstrating a significant reduction of target lesions (approximately 32% compared to baseline) 6 weeks after reintroduction of etoposide and cisplatin. Left: tumor scans after RRx-001. Right: tumor scans after etoposide and cisplatin treatment.