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Remarkable response to a novel ATR inhibitor in a patient with poorly differentiated neuroendocrine carcinoma.

Yoshihito David Saito[a], Zaibo Li[b], Maryam Lustberg[a], Cassandra Grenade[a], Robert Wesolowski[a,*]

[a] Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
[b] Department of Pathology, The Ohio State University Comprehensive Cancer Center, USA

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ABSTRACT

M6620 (formerly known as VX-970) is a potent inhibitor of ataxia telangiectasia and Rad3-related protein (ATR), a serine/threonine-specific protein kinase involved in activation of checkpoint signaling and promotion of cell cycle arrest in response to DNA damage (inhibition constant [Ki] < 300 pM, IC50 of 20 nM). ATR inhibition enhances the cytotoxic effect of DNA damaging drugs and infrared radiation (IR) in many cancer cell lines and primary human tumors. M6620 is currently under investigation in early-phase clinical trials for the treatment of a number of malignancies. Below, we report a case of a patient with metastatic prostate cancer with clonal evolution to poorly differentiated large cell neuroendocrine carcinoma who developed an exceptional response to treatment with M6620 and cisplatin on a phase I trial VX12-970-001 (NCT02157792: An Open-Label, First-in-Human Study of the Safety, Tolerability, and Pharmacokinetics of VX-970 in Combination With Cytotoxic Chemotherapy) with over 20 months of non-CNS progression free survival. We will discuss the mechanism of action of M6620, rationale for enrolling the patient in this trial and hypothesize the reasons for this exceptional response.

1. Introduction

Neuroendocrine differentiation represents a subset of prostate cancer that is more commonly seen in the metastatic setting. There is an increasing understanding that neuroendocrine differentiation is a mechanism of resistance in prostate cancer and is associated with use of androgen deprivation therapy. [1] This entity is referred to as treatment-emergent neuroendocrine prostate cancer (t-NEPC) and may involve from 30% to 40% of patients with metastatic, castrate-resistant prostate cancer. [2] T-NEPC carries an overall dismal prognosis with a median survival of about 1 year with standard of care therapy. Survival of patients following front line treatment with platinum and etoposide regimen is even more dismal with a median survival of 7 months. [3] Therefore, there is an unmet need to develop more effective treatments for this disease.

For patients with t-NEPC, the combination of carboplatin and etoposide is most commonly used in the first-line setting. However, despite displaying initial sensitivity and clinical response to this regimen, the disease invariably develops secondary resistance and progresses quickly. Following development of secondary resistance to front line therapy, subsequent lines of treatment have very modest anti-tumor activity.

An important mechanism by which tumor cells are protected from excessive DNA damage is the DNA damage response (DDR) pathway which is regulated by homologous kinases, ataxia telangiectasia mutated (ATM) and ataxia telangiectasia mutated and Rad3-related protein (ATR). In healthy cells, ATR and ATM function in parallel in response to DNA damage. ATR is a serine/threonine kinase that is activated in response to the presence of single-stranded DNA breaks arising at stalled replication forks or through the processing of double-strand breaks, in nucleotide excision repair as well as homologous recombination repair. [4] Activation of ATR leads to downstream signaling that ultimately results in cell cycle arrest. ATM, like ATR, is a serine/threonine kinase that functions as an apical regulator of DDR but is instead primarily activated in response to double-strand DNA breaks which is generated through a variety of insults including ionizing radiation or topoisomerase inhibition. [5] In many malignant cells, loss of ATM or p53 signaling is common. [6] While defects in DDR components may potentially confer a growth advantage for cancer cells via permissive cellular growth in the face of oncogene-induced replicative stress, they also promote oncogenic addiction to the remaining, intact DDR pathways to survive DNA damage. In malignancies that harbor such deficiencies in DDR pathways, targeting the remaining, intact DDR pathways may lead to synthetic lethality.

* Corresponding author.
E-mail address: Robert.Wesolowski@osumc.edu (R. Wesolowski).

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To this end, there has been increasing interest in development of inhibitors of ATR in the treatment of ATM or p53 deficient malignancies. [7,8] M6620 (previously known as VX-970) is a highly potent and selective inhibitor of ATR with Ki of < 200 pM. [9,10] M6620 was developed from identification of a lead candidate compound from high-throughput screening (HTS) studies and lead optimization by a combination of structure-activity relationship (SAR) and homology modeling studies. [11]

The addition of DNA-damaging chemotherapy or ionizing radiation (IR) can potentially impart additional genotoxic stress and thereby potentiate the synthetic lethality of ATR inhibitors. *In vitro* studies have demonstrated that exposure of cell lines deficient in ATM to ATR inhibitors dramatically increased the toxicity of cisplatin or IR whereas this synergy was absent in non-ATM deficient cell lines. [9–11] In a xenograft model utilizing severe combined immune deficiency (SCID) mice with implanted non-small cell lung carcinoma (NSCLC) tumors, M6620 was demonstrated to enhance the sensitivity to cisplatin. In particular, M6620 was found to have optimal synergy when dosed approximately 24 h after the dose of DNA damaging chemotherapy. Notably, in several of the xenografts that demonstrated initial insensitivity to cisplatin, the addition of M6620 led to complete tumor growth inhibition. In contrast, in vitro studies also showed that non-malignant cells were able to tolerate ATR inhibition via an intact ATM-p53 pathway. [12,13]

Here, we have described a patient who developed metastatic high-grade t-NECP harboring a somatic mutation in *BRCA 2* gene and duplication of exons 1–3 in *ATR* gene. The patient was initially treated with carboplatin-etoposide doublet chemotherapy and then experienced a remarkably long and durable response of nearly 2 years to ATR inhibition with M6620 in combination with cisplatin.

2. Case report

The patient is a 53-year old male who underwent a robotic prostatectomy and retroperitoneal lymph node dissection in 2012 which showed pT4 pN0 adenocarcinoma with a Gleason score of 4 + 5 = 9. Margins were microscopically positive and peri-neural invasion was present. Initial prostatic-serum antigen level (PSA) was reported at 26. PSA failed to fall to undetectable levels and patient was therefore treated with androgen blockage with gonadotropin releasing hormone agonist triptorelin and androgen receptor inhibitor bicalutamide. Within 4 months of therapy, his PSA levels began to rise and in the summer 2013 the patient was started on bicalutamide withdrawal. He remained on triptorelin until summer of 2015. Staging scans in late 2014 demonstrated pelvic sidewall adenopathy as well as scapular and bilateral iliac sclerotic lesions felt to be consistent with metastatic disease. The patient was then treated with palliative docetaxel and prednisone. Restaging evaluation after 6 cycles continued to demonstrate stable left pelvic sidewall adenopathy and sclerotic bone lesions. The patient was doing well and his PSA became undetectable.

Four months later, in early 2015, the patient developed progressive back pain and a computed tomography (CT) scan showed significant evidence of progression with increasing lymphadenopathy along the left pelvic wall, osteoblastic lesions in the iliac bone, L5 and innumerable metastatic disease throughout the liver. CT-guided liver biopsy revealed hepatic parenchyma infiltrated by monotonous sheets of high-grade neoplastic cells with high nuclear cytoplasmic ratio, fine chromatin and variable amount of cytoplasm. Immunohistochemical stains were strongly positive for synaptophysin. Mitotic count was 153 mitoses per 10 high power fields and Ki-67 was greater than 80%. The combined histomorphologic and immunophenotypic findings were consistent with high-grade neuroendocrine carcinoma.

The patient was subsequently started on palliative radiotherapy to the left hemi-pelvis and the right iliac wing with 20 Gray in 5 fractions with subsequent improvement in his back pain. Following radiation therapy, he started palliative treatment with carboplatin and etoposide.

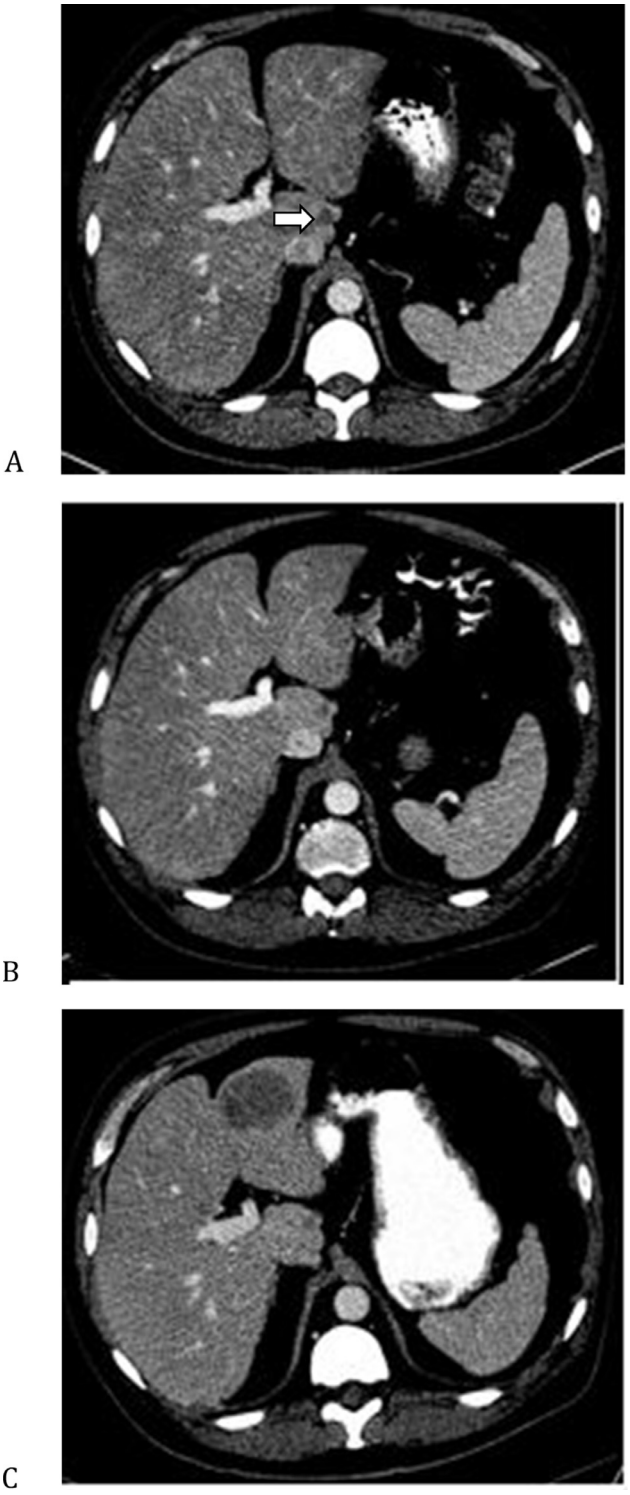

Fig. 1. Computed tomography (CT) scan of the abdomen at baseline, after cycle 4 and at the time of progression after cycle 23 in the index case. The scan demonstrates a small liver lesion in the caudate lobe initially measuring 1.1 × 1.2 cm prior to treatment with M6620 and cisplatin (A, see white arrow). After 4 cycles of therapy, the lesion measures 0.8 × 1.0 cm (B). After completion of 23 cycles, a new, large anterior left hepatic lobe lesion measuring 4.5 × 4.1 cm is identified (C).

He initially had a good response to treatment with scans after cycle 2 showing improved appearance of liver and osteoblastic lesions involving the spine and pelvis. After completion of 6 cycles, restaging scans showed stable disease.