Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Left Kidney Undifferentiated Spindle Cell Sarcoma with Myeloid Cell Leukemia-1 Amplification: Therapeutic Response to Bortezomib, Venetoclax, and Dexamethasone Therapy

Cheng-Yu Tang[1,2], Chueh-Chuan Yen[2,3,4,5]*

[1]Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
[2]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3]Division of Clinical Research, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
[4]Division of Medical Oncology, Center for Immuno-oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
[5]Institute of Biopharmaceutical Sciences, College of Pharmaceutical Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan

Abstract

The overexpression of myeloid cell leukemia-1 (MCL-1) has been identified in numerous hematologic malignancies and solid tumors. Currently, there are no selective MCL-1 inhibitors. Here, we present a case of left kidney undifferentiated spindle cell sarcoma with MCL-1 amplification. The tumor showed primary resistance to chemotherapy and immune checkpoint inhibitors. Combination therapy of bortezomib, venetoclax, and dexamethasone demonstrated a positive response, resulting in a stable tumor condition for 6 months. To our knowledge, this is the first report to mention the clinical efficacy of bortezomib, venetoclax, and dexamethasone therapy in an MCL-1-amplified solid tumor.

Keywords: Bortezomib, myeloid cell leukemia-1 amplification, sarcoma, venetoclax

Introduction

Chemotherapeutic drugs and radiation therapy induce deoxyribonucleic acid (DNA) damage and promote apoptosis in tumor cells. However, the apoptotic process is often disrupted in tumor cells, leading to chemoresistance and radioresistance.[1,2] The intrinsic apoptotic pathway is a process which initiates with intracellular signals. It is controlled by the B-cell lymphoma 2 (BCL-2) protein family and is mediated through mitochondrial outer membrane permeabilization (MOMP). Upon the activation of MOMP, intermembrane space proteins are released into the cytoplasm, promoting the formation of apoptosomes and leading to the activation of caspases and apoptosis.[3] Myeloid cell leukemia-1 (MCL-1) protein belongs to the BCL-2 protein family and shows antiapoptotic activity, and the overexpression of MCL-1 is frequently observed in hematologic malignancies and various solid tumors.[4,5] Herein,

Submitted: 25-Jul-2023 **Revised:** 03-Sep-2023
Accepted: 05-Oct-2023 **Published:** 26-Dec-2023

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/ejcrp.eJCRP-D-23-00026

Address for correspondence: Prof. Chueh-Chuan Yen, Division of Clinical Research, Department of Medical Research, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Beitou Dist., Taipei 11217, Taiwan.
E-mail: ccyen@vghtpe.gov.tw

How to cite this article: Tang CY, Yen CC. Left kidney undifferentiated spindle cell sarcoma with myeloid cell leukemia-1 amplification: Therapeutic response to bortezomib, venetoclax, and dexamethasone therapy. J Cancer Res Pract 2023;10:154-7.

we present a case of sarcoma with MCL-1 amplification who had a positive response to combination treatment with bortezomib, venetoclax, and dexamethasone.

Case Report

A 60-year-old male presented with persistent left-sided chest pain for 1 month. He was a current smoker who had smoked one pack of cigarettes per day for 30 years. He had no previous medical conditions. One month before hospitalization, he experienced left-sided chest pain, low back pain, dyspnea on exertion, poor appetite, and a weight loss of 7 kg over 6 months. Chest and abdominal computed tomography revealed a 9-cm soft-tissue mass in the left kidney, with left pleural seeding, moderate left pleural effusion, and metastasis to the right lower lung and left adrenal gland [Figure 1a-c]. An ultrasound-guided biopsy of the left kidney tumor indicated undifferentiated spindle cell sarcoma, Grade 2. The tumor was immunoreactive for CD34 and negative for mouse double minute 2 homolog, cyclin-dependent kinase 4 (CDK4), melan-A, cathepsin K, cytokeratin, h-caldesmon, actin, and signal transducer and activator of transcription 6. A whole-body bone scan did not detect any bone metastasis. The final diagnosis was undifferentiated spindle cell sarcoma of the left kidney, Stage IV. He received one cycle of epirubicin and ifosfamide combination chemotherapy; however, the tumor progressed rapidly. As a second-line treatment, he received pembrolizumab, paclitaxel, and cisplatin. Palliative radiation therapy was also administered to the left kidney tumor mass. Next-generation sequencing (NGS) was performed on the tumor sample, which revealed single-nucleotide variant of polybromo-1 (PBRM1) and retinoblastoma gene (RB1), amplification of MCL1, neurotrophic receptor tyrosine kinase 1, and nibrin, homozygous deletion of tumor protein P53, and heterozygous deletion of F-box/WD repeat-containing protein 7, cyclin-dependent kinase inhibitor 2A (CDKN2A), checkpoint kinase 1 (CHEK1), ataxia-telangiectasia mutated protein kinase, RB1, and breast cancer gene 2. The tumor mutation burden was 1.3 mutations per megabase, and microsatellite stability was observed [Table 1]. The tumor progressed after one cycle of second-line treatment as seen in chest and abdominal computed tomography [Figure 1d-f], prompting the initiation of third-line treatment with bortezomib, venetoclax, and dexamethasone based on the NGS report. The left pleural effusion decreased, and the patient experienced a significant improvement in dyspnea, eliminating the need for supplemental oxygen. The only notable adverse

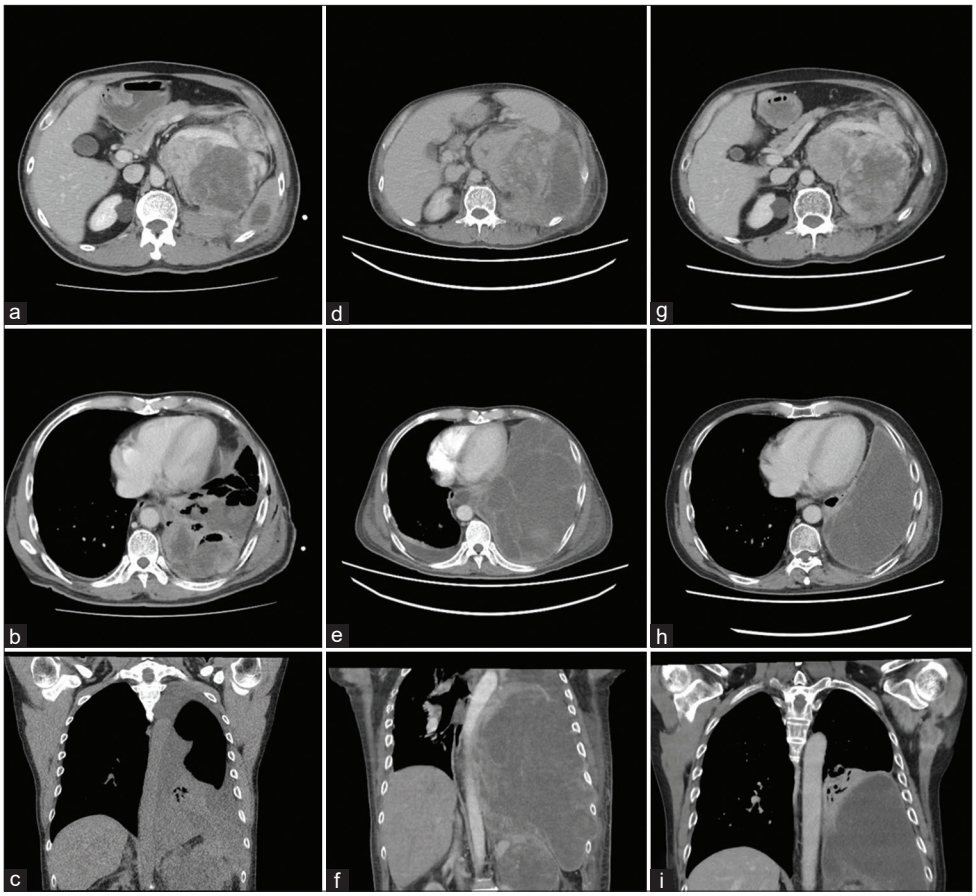

Figure 1: Serial computed tomography images revealed the initial presentation of a left kidney mass, pleural seeding, and left pleural effusion (a-c). Following two cycles of chemotherapy, left pleural seeding and effusion progressed, resulting in displacement of the thoracic aorta and esophagus toward the right side (d-f). After 6 months of treatment with bortezomib, venetoclax, and dexamethasone, the amount of left pleural effusion decreased, and the thoracic aorta and esophagus returned to their normal positions (g-i)

Table 1: Next-generation sequencing result

Single nucleotide variants	Allele frequency (%)	
PBRM1 F1045fs	55.5	
RB1 splice donor	54.4	
Copy number alteration	**Chromosome**	**Copy number**
MCL1	1	7
NTRK1	1	7
NBN	8	7
TP53	17	0
FBXW7	4	1
CDKN2A	9	1
CHEK1	11	1
ATM	11	1
RB1	13	1
BRCA2	13	1

Tumor mutational burden: 1.3 mutations per megabase, microsatellite instability: Microsatellite stable, fusion results: Not detected.
BRAC2: Breast cancer gene 2, RB1: retinoblastoma gene, ATM: Ataxia-telangiectasia mutated protein kinase, CHEK1: checkpoint kinase 1, CDKN2A: Cyclin-dependent kinase inhibitor 2A, FBXW7: F-box/WD repeat-containing protein 7, TP53: Tumor protein P53, NBN: Nibrin, NTRK1: Neurotrophic receptor tyrosine kinase 1, MCL-1: Myeloid cell leukemia-1, PBRM1: Polybromo-1

event during treatment was mild hyperthermia with sweating after each cycle of bortezomib. The tumor remained stable after 6 months of treatment with bortezomib, venetoclax, and dexamethasone [Figure 1g-i].

Discussion

This patient presented with a sarcoma of the left kidney that was initially resistant to standard chemotherapy and immune checkpoint inhibitors. Genetic alterations of PBRM1, TP53, and MCL-1 were identified based on the NGS results. PBRM1 mutation, the second most common mutation in renal cell carcinoma (RCC), was detected in the sarcoma. Previous studies have identified the PBRM1 mutation as a potential predictor of immunotherapy response in RCC, although the results have been inconsistent. However, our patient did not benefit from pembrolizumab treatment.[6] TP53, known as the "guardian of the genome," plays a crucial role in responding to DNA damage and initiating the apoptotic process. Tumors with TP53 mutations are commonly associated with chemoresistance and radioresistance.[7] Currently, there is no effective treatment specifically targeting TP53-mutated cancer.

The intrinsic apoptotic pathway is controlled by the BCL-2 protein family which can be classified into three groups: effectors, antiapoptotic proteins, and BCL-2 homology 3 (BH3-only) proteins. Effectors, mainly BCL-2-associated X protein and BCL-2 antagonist/killer (BAK), are the most important members of the BCL-2 protein family. They exhibit proapoptotic activity, and are involved in MOMP execution, which is the key step in the intrinsic apoptotic pathway. BCL-2 and MCL-1 are antiapoptotic proteins that inhibit the effectors and are regulated by BH3-only proteins such as phorbol-12-myristate-13-acetate-induced protein 1 (Noxa). Bortezomib, the first proteasome inhibitor and one of the main treatments for myeloma and mantle cell lymphoma, indirectly downregulates MCL-1 by inducing Noxa and preventing Noxa degradation. Noxa directly downregulates MCL-1 and leads to the activation of the effector BAK.[4,8] However, in mantle cell lymphoma, bortezomib resistance can be caused by higher levels of BCL-2.[9] Punnoose *et al*. investigated the use of venetoclax, a BH3-mimetic/BCL-2 inhibitor, in myeloma and lymphoid malignancy treatment, and found that a high level of MCL-1 was strongly correlated with venetoclax resistance.[10] In addition, they demonstrated that the balance between MCL-1 and BCL-2 determined the sensitivity and resistance to MCL-1 and BCL-2 inhibitors. They further hypothesized that dual MCL-1 and BCL-2 inhibition may overcome resistance and induce synergistic proapoptotic effects, and thus cotreated myeloma cells with venetoclax and bortezomib, and a durable response was observed without early progression.[10] The synergistic proapoptotic effect of bortezomib and venetoclax has also been observed in sarcoma cells.[4] Glucocorticoids also target the intrinsic apoptotic pathway and exert a proapoptotic effect.[11] Previous studies have shown that the expressions of BCL-2 and MCL-1 may correlate with glucocorticoid sensitivity. In a lymphoma cell line study, BCL-2 overexpression was shown to potentially attenuate glucocorticoid-induced apoptosis and cause glucocorticoid resistance, and in a chronic lymphocytic leukemia study, a high MCL-1 expression was more frequently observed in nonresponders treated with chlorambucil–prednisone than in responders.[12,13] Currently, the clinical efficacy of venetoclax plus bortezomib and glucocorticoid has only been studied in myeloma. The BELLINI phase 3 trial demonstrated the progression-free survival (PFS) benefit of venetoclax plus bortezomib and dexamethasone (BVD) in patients with relapsed or refractory multiple myeloma, although overall survival did not improve due to a higher risk of infection.[14] In addition, a high BCL-2 expression predicted the PFS benefit of BVD treatment in subgroup analysis.

In our case, MCL-1 amplification was identified in the sarcoma. However, MCL-1 amplification is not equivalent to MCL-1 overexpression. Immunohistochemistry of MCL-1 or BCL-2 was not performed in our case, and we so could not determine whether MCL-1 or BCL-2 was overexpressed. There is currently no standard treatment for such a refractory case; thus, MCL-1-targeted therapy could be a reasonable next-line treatment option. Since selective MCL-1 inhibitors were not available, we started BVD treatment by referring to the BELLINI myeloma trial, with modifications of the dosage and schedule based on the physician's experience and the patient's performance status.[15] No previous report has discussed BVD treatment in patients with solid tumors. Surprisingly, our patient had a good response with stable disease for over 6 months. This report highlights the clinical benefit of BVD treatment in a patient with refractory sarcoma, and we suggest that MCL-1 amplification could be a potential

biomarker to predict the response to BVD treatment. More clinical experience and studies are necessary to determine the efficacy of BVD treatment in MCL-1-amplified or overexpressed sarcoma or solid tumors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
2. Goto A, Kanda H, Ishikawa Y, Matsumoto S, Kawaguchi N, Machinami R, *et al.* Association of loss of heterozygosity at the p53 locus with chemoresistance in osteosarcomas. Jpn J Cancer Res 1998;89:539-47.
3. Vringer E, Tait SW. Mitochondria and cell death-associated inflammation. Cell Death Differ 2023;30:304-12.
4. Weller S, Toennießen A, Schaefer B, Beigl T, Muenchow A, Böpple K, *et al.* The BCL-2 inhibitor ABT-199/venetoclax synergizes with proteasome inhibition via transactivation of the MCL-1 antagonist NOXA. Cell Death Discov 2022;8:215.
5. D'Aguanno S, Del Bufalo D. Inhibition of anti-apoptotic Bcl-2 proteins in preclinical and clinical studies: Current overview in cancer. Cells 2020;9:1287.
6. Miao D, Margolis CA, Gao W, Voss MH, Li W, Martini DJ, *et al.* Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. Science 2018;359:801-6.
7. Hientz K, Mohr A, Bhakta-Guha D, Efferth T. The role of p53 in cancer drug resistance and targeted chemotherapy. Oncotarget 2017;8:8921-46.
8. Gomez-Bougie P, Wuillème-Toumi S, Ménoret E, Trichet V, Robillard N, Philippe M, *et al.* Noxa up-regulation and Mcl-1 cleavage are associated to apoptosis induction by bortezomib in multiple myeloma. Cancer Res 2007;67:5418-24.
9. Luanpitpong S, Janan M, Yosudjai J, Poohadsuan J, Chanvorachote P, Issaragrisil S. Bcl-2 family members BCL-XL and Bax cooperatively contribute to bortezomib resistance in mantle cell lymphoma. Int J Mol Sci 2022;23:14474.
10. Punnoose EA, Leverson JD, Peale F, Boghaert ER, Belmont LD, Tan N, *et al.* Expression profile of BCL-2, BCL-XL, and MCL-1 predicts pharmacological response to the BCL-2 selective antagonist venetoclax in multiple myeloma models. Mol Cancer Ther 2016;15:1132-44.
11. Schmidt S, Rainer J, Ploner C, Presul E, Riml S, Kofler R. Glucocorticoid-induced apoptosis and glucocorticoid resistance: Molecular mechanisms and clinical relevance. Cell Death Differ 2004;11 Suppl 1:S45-55.
12. Bortner CD, Oakley RH, Cidlowski JA. Overcoming apoptotic resistance afforded by Bcl-2 in lymphoid tumor cells: A critical role for dexamethasone. Cell Death Discov 2022;8:494.
13. Saxena A, Viswanathan S, Moshynska O, Tandon P, Sankaran K, Sheridan DP. Mcl-1 and Bcl-2/Bax ratio are associated with treatment response but not with Rai stage in B-cell chronic lymphocytic leukemia. Am J Hematol 2004;75:22-33.
14. Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, *et al*. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): A randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2020;21:1630-42.
15. Wang H, Guo M, Wei H, Chen Y. Targeting MCL-1 in cancer: Current status and perspectives. J Hematol Oncol 2021;14:67.