

Case Report

Therapy of Angiosarcoma with Thalidomide and Lenalidomide

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Keywords

Angiosarcoma · Lenalidomide · Thalidomide

Abstract

Angiosarcoma is an uncommon malignancy with a poor prognosis. Systemic therapy options for patients with metastatic disease generally have limited effectiveness. In this case study, a 73-year-old male with metastatic angiosarcoma who previously declined chemotherapy and developed progressive disease after checkpoint inhibitor immunotherapy elected to try thalidomide based on 6 case reports describing its effectiveness. Thalidomide resulted in stable disease for 9 months, but due to severe neuropathy as a side effect, lenalidomide was then substituted for thalidomide. The patient continued to have stable disease on lenalidomide for an additional 16 months and ongoing. This is the first case study to report on effective treatment of angiosarcoma with lenalidomide. Further investigation of lenalidomide in the management of angiosarcoma is warranted.

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Published by S. Karger AG, Basel

Introduction

Angiosarcomas are uncommon tumors arising from endothelial cells of lymphatic or vascular origin, most commonly in the head and neck or breast. The prognosis is generally poor due to early metastatic spread, with 5-year overall survival for all comers of 30%. A variety of chemotherapeutic agents (e.g., paclitaxel, docetaxel, and gemcitabine) and targeted agents

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(e.g., sorafenib, sunitinib, and bevacizumab) have been utilized in its management, but with relatively low response rates [1]. Several case reports describe thalidomide as an effective agent [2–5], though it has never been assessed in a prospective clinical trial. Thalidomide is referred to as an immunomodulator, but its mechanism of action is complex. The next-generation agent lenalidomide has, in a case report, been shown to have efficacy against hepatic epithelioid hemangioendothelioma, a related vascular tumor [6]. In this study, by chance, it was demonstrated that temporary stoppage of the drug resulted in renewed growth of the tumor, which ended when drug treatment was resumed. The use of lenalidomide has never been described in the management of angiosarcoma. In this case report, we describe a patient who had stable disease for 9 months on thalidomide and then 16 months on lenalidomide, with ongoing response.

Case Report

A 70-year-old male with no known risk factors for angiosarcoma presented with dysphagia and was found on MRI of the neck to have a 2.5-cm enhancing right infratemporal mass and a 2.5-cm right level II lymph node. He underwent surgical resection. The tumor was densely adherent to adjacent structures including blood vessels, but complete removal was attempted. Pathology demonstrated a 2.5-cm high-grade epithelioid angiosarcoma, resected with positive margins, and 5/17 positive lymph nodes, the largest of which was 2.8 cm and was associated with extranodal extension. The tumor genome was analyzed by the Laboratory of Diagnostic Molecular Pathology at Memorial Sloan-Kettering Cancer Center. MSK-IMPACT was used to identify mutations in 468 genes. Results were no mutations, no copy number alterations, and no structural variants detected. The microsatellite DNA was stable. Gene fusions were investigated by the Archer FusionPlex Custom Solid Panel. Sixty-two genes were investigated. Of these, 1 fusion was detected, PTBP1-MAML2, which is of unknown significance. The patient's postoperative course was complicated by a pulmonary embolism, right internal carotid artery hemorrhage which was coiled by interventional radiology, and pneumonia from aspirating blood at the time of the hemorrhage. After a prolonged hospital admission, he was discharged to a nursing facility, severely deconditioned, with a gastrostomy tube for feeding due to persistent dysphagia, but otherwise neurologically intact. He has continued on Xarelto since discharge.

PET/CT 7 weeks postoperatively revealed 1 subcm lung nodule (max SUV 8.8) and bilateral hilar nodes (max SUV 5.8). He was offered chemotherapy, but due to his continued poor functional status, he elected for adjuvant radiation therapy to the neck, followed by combined checkpoint inhibitor immunotherapy on a clinical trial. He received a total dose of 74 Gy proton radiation therapy, followed by 4 cycles of ipilimumab and nivolumab. The only complication from the immunotherapy was lower extremity edema. After 4 months of immunotherapy, his PET/CT showed progression of disease. Still hesitant to undergo chemotherapy due to concerns over relatively poor efficacy and likely toxicity, the patient wanted to try thalidomide, based on 5 case reports, 2–5 the earliest being from 2003. Not without some difficulty, he found a medical oncologist willing to give him thalidomide, reluctantly. Starting at 150 mg/day, the dose was increased to 200 mg/day after approximately 6 weeks. Since beginning thalidomide, he has had stable disease on subsequent PET/CT scans (Fig. 1). Following the PET/CT scan after 3 months on thalidomide, he underwent a dose reduction to 50 mg/day due to worsening peripheral neuropathy (edema of extremities and problems with gait) and ultimately was switched to lenalidomide (10 mg/day), after about 9 and a half months on thalidomide, as he had continued stable disease but worsening neuropathy. The neuropathy was diagnosed by concentric needle electromyography and nerve conduction studies as well as clinical symptoms and was classified as moderate-to-severe chronic, generalized sensorimotor

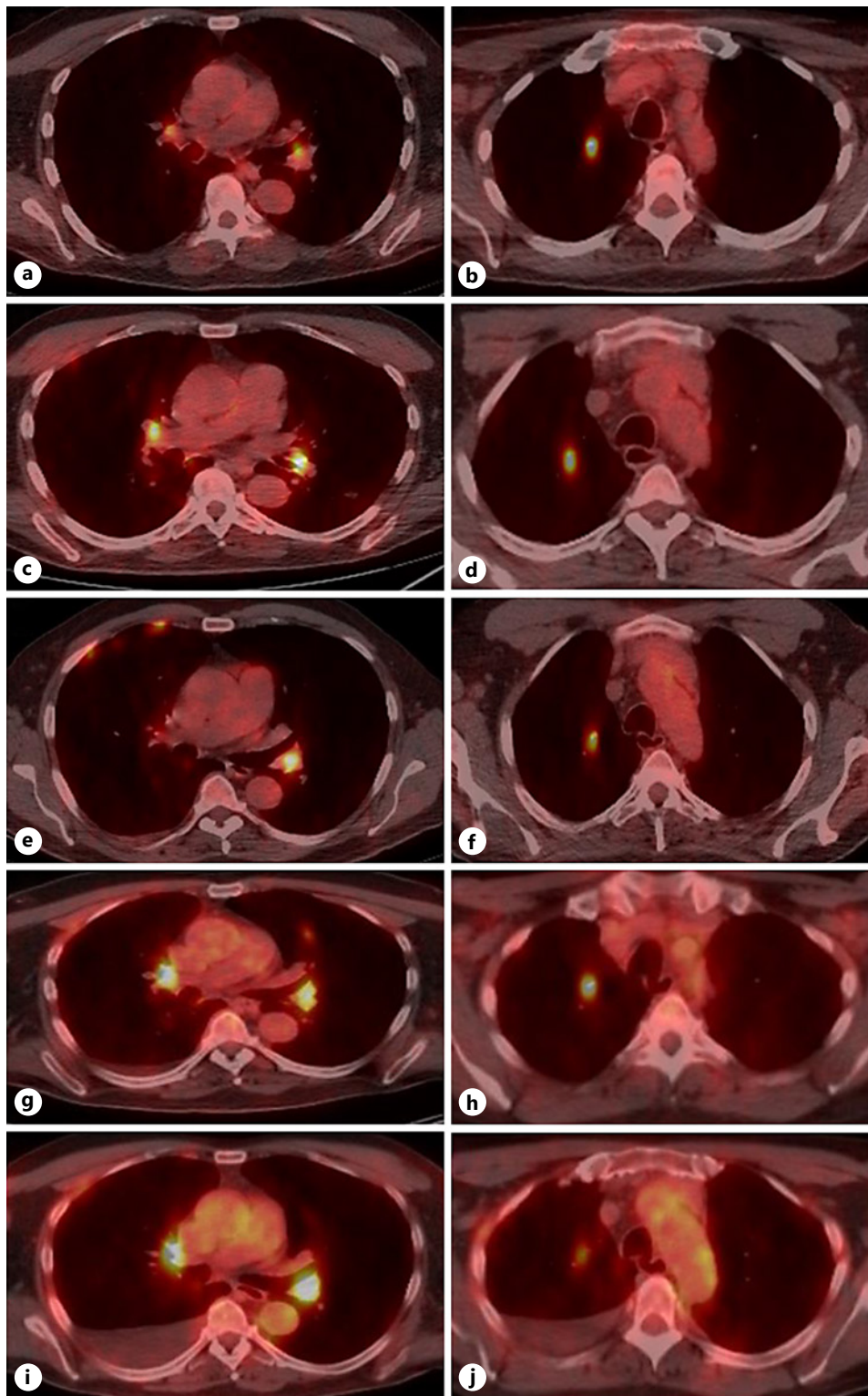
polyneuropathy with predominantly axonal features. He continues to have stable disease 16 months after starting lenalidomide. The tumor cells remain metabolically active, as indicated by FDG avidity on PET, but there has been no growth of the tumor since initiation of thalidomide treatment (Fig. 1). The patient remains asymptomatic with excellent performance status, except for the persistent neuropathy.

Discussion

Thalidomide and lenalidomide are closely related molecules that function via binding to the protein cereblon, which participates in the ubiquitin pathway, a major regulator of protein turnover in cells [7]. The clinical use of the drugs, as well as the potential mechanism of action, was recently reviewed [8]. These drugs are very weakly cytotoxic to tumor cells, if at all. The ubiquitin pathway acts on hundreds or thousands of proteins, including multiple transcription factors, so modification of the ubiquitin pathway has multiple effects in the cell, but it is important to emphasize that the drugs are very selective in their effects. Thus, while thalidomide was found to have devastating effects on a developing human fetus, it had very minor side effects on the mother, which is why it was extensively used for some time as a treatment for morning sickness in pregnant women in Europe (before its effect on the fetus was recognized). Fetuses were often born without arms or legs, and the mechanism appears to be the inhibition of the growth of blood vessels in the developing extremities.

Thalidomide was subsequently tested for therapy of multiple myeloma and rapidly became part of the standard of care for this malignancy. The original use of thalidomide for multiple myeloma was based on the known antiangiogenic effect of the drug, together with the observation that aggressive myeloma was associated with new blood vessel development in the bone marrow, but this rationale may not explain its efficacy. Thalidomide was subsequently replaced by its derivative lenalidomide, primarily because the latter less commonly caused the neuropathy that was very frequent after months of thalidomide treatment. Lenalidomide was tested on a wide variety of solid tumors [9], but under limited circumstances (near-terminal patients who had failed all other treatments) and using a response rate endpoint that is inherently less relevant to a drug like lenalidomide that is probably more cytostatic than cytotoxic. In these trials, “stable disease” was common, but few responses were noted, and they were not considered striking enough for further evaluation. This report emphasizes the fact that “stable disease” constitutes effective therapy. Lenalidomide was evaluated more thoroughly on other tumors of the B-lymphocyte lineage, and effectiveness for certain B-cell lymphomas was established [10]. Considerable progress has been made in elucidating the mechanism of action of lenalidomide. It was demonstrated that lenalidomide, via binding to cereblon, affects the level of transcription factors c-Myc and IRF4, which regulate lymphoid cell growth [11]. These drugs have generally been referred to as “immunomodulatory” drugs. Although they do modulate the immune system, it seems to us unlikely that this is the mechanism of action against tumors.

Fig. 1. PET/CT scans (**a, b**) at baseline prior to the start of immunotherapy showing hilar lymph nodes and right apical lung nodule index lesions; (**c, d**) after 4 cycles of immunotherapy with increased SUV of the right apical lung nodule from 6.2 to 11.7, increased SUV of hilar nodes from 4.7 to 6.7, and increased size of 2 additional subcm lung nodules and 1 new subcm hilar node (not shown). Thalidomide was started just afterward; (**e, f**) 3 months after starting thalidomide, stable disease; (**g, h**) 9 months after starting thalidomide, right before switching to lenalidomide. This scan (and all subsequent ones) was done at a different location, making precise comparison with previous scans difficult, since there is a higher background uptake throughout the scan; (**i, j**) 16 months after starting lenalidomide, showing stable disease in hilar nodes and lung nodules.
(For figure see next page.)



Further studies are required to confirm the effectiveness of lenalidomide on angiosarcoma. If this is confirmed, it might tentatively be explained by the known antiangiogenesis effect of the drug. However, considering that angiosarcoma and the B-lymphocyte malignancies are not closely related and there is no known reason why lenalidomide would be

selectively effective on only these tumor types, other possible mechanisms must be considered. If lenalidomide functions by modifying the production of growth factors, it might be active on other tumors that require growth factors, which probably includes a wide variety of tumors. The 7 case reports since 2003 suggesting a benefit of thalidomide or lenalidomide, as well as the current report, warrant further investigation. This appears to be the first case in which lenalidomide was used for angiosarcoma. By initiating therapy with lenalidomide, in future studies, the toxicity due to thalidomide can be avoided. The astronomical cost of Revlimid in the USA makes it difficult to use it off-label, since health insurance companies will not cover the cost. However, the Celgene Patient Support program is helpful. Also, generic lenalidomide is available in much of the world, including India, where the cost is about 300 times less than the cost of branded lenalidomide (Revlimid) in the USA, so it might be simplest to do unfunded investigator-initiated trials in other countries.

Statement of Ethics

Ethical approval was not required. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

We certify that the authors listed here have no affiliations with or involvement in any organizations and/or any financial interest.

Author Contributions

M.J.M., J.A.M., M.D.M., and R.G. conducted the conception and design of the manuscript. M.J.M., R.G., and M.D.M. were involved in collection and assembly of data, data analysis, and interpretation. M.J.M. and M.D.M. drafted the manuscript. R.G. was involved in patient care. All authors were involved in manuscript editing and review and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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