American Journal of Cancer Case Reports

American Journals of
Cancer Case Reports
http://ivyunion.org/index.php/ajccr/
Vol. 1, Article ID 201300114, 6 pages

Case Report

Successful Rechallenge with Vemurafenib and Corticosteroids in a Patient with Vemurafenib Induced Liver Dysfunction, Previously Treated with Ipilimumab

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Abstract

Introduction: There are multiple new systemic therapies for patients with metastatic melanoma, including vemurafenib and ipilimumab. Because of this, more patients will be exposed to multiple medicines during their treatment course. Here we present the case of a successful rechallenge with vemurafenib and concurrent corticosteroids in a patient with vemurafenib responsive metastatic melanoma and vemurafenib induced liver dysfunction thought to be related to previous treatment of ipilimumab.

Presentation of case: A 60-year-old woman presented with metastatic melanoma to her liver and lymph nodes with normal liver function tests (LFTs) and was started on ipilimumab. With rapid disease progression despite ipilimumab, treatment was switched to vemurafenib. She experienced quick and good regression in her disease burden but subsequently experienced a grade 4 elevation in her LFTs, which resolved with a corticosteroid taper. Her disease responded well to a vemurafenib rechallenge at a reduced dose; however, she experienced another increase in her LFTs. By administering vemurafenib with corticosteroids concurrently, she achieved good tumor shrinkage without liver dysfunction.

Conclusion: While not all drug related liver toxicity has been shown to be responsive to corticosteroids, for patients previously treated with ipilimumab who experience elevated LFTs while on vemurafenib, re-challenging with a reduced dose of vemurafenib and concurrent corticosteroids treatment may be tried with the goal of maintaining good clinical efficacy and controlling liver dysfunction.

Keywords: Melanoma; Vemurafenib; Ipilimumab; Corticosteroids; Hepatotoxicity

Peer Reviewers: Nian-feng Sun, MD, PhD, Qilu Hospital, Shandong University, China; Bilal Cetin, MD. Department of Otolaryngology Head and Neck Surgery, Gumussuyu Military Medical Hospital, Turkey

Received: March 11, 2012; **Accepted**: April 14, 2013; **Published:** May 14, 2013

Competing Interests: The authors have declared that no competing interests exist.

Consent: The patient has given informed consent for the case report to be published.

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Introduction

Multiple systemic treatments for metastatic melanoma have recently been approved, including vemurafenib and ipilimumab, with many more in development. As more patients with metastatic melanoma receive treatment with these medicines, the number of patients exposed to multiple new systemic therapies at some point during their treatment course will increase, with the potential for an emerging adverse event profile associated with temporally separate exposures. We present the case of a 60 year old female with vemurafenib responsive metastatic melanoma and a previous exposure to ipilimumab who developed a Grade 4 hepatitis while on vemurafenib who was successfully managed with concurrent vemurafenib and corticosteroid treatment.

Case Report

A 60 year old Caucasian female with a past medical history of hypothyroidism was diagnosed with melanoma in situ in 2008, excised with a 1 cm margin. Upon resection, the surgical margins were clear. In 2009, she had a recurrence in her left upper flank. Restaging positron emission tomography/computed tomography (PET/CT) scan demonstrated multiple nodules in the left flank and in the axilla. She subsequently underwent full left axillary lymphadenectomy and adjuvant XRT, followed by high dose adjuvant Interferon therapy for resected stage IIIb disease. Her follow up PET/CT scan 6 months from the completion of interferon was unremarkable but the 12 months post interferon PET/CT scan showed multiple liver and subcutaneous nodules. Biopsy of skin and genetic analysis revealed BRAF V600E mutation positive metastatic melanoma. The patient was initially started on ipilimumab 3 mg/kg IV every 3 weeks, hoping for sustainable response given her relatively asymptomatic disease. Although she did not experience any significant side effects, after 2 cycles of treatment her disease dramatically progressed and she became symptomatic. Vemurafenib 960 mg BID was initiated 1 week after her last dose of ipilimumab with good clinical response. 3 weeks after starting treatment with vemurafenib, the patient developed a moderate skin rash and her dose was reduced to 720mg BID. Despite this reduction, a grade 3 elevation (AST=504 IU, ALT=328 IU) in her LFTs was detected at 6 weeks into treatment with vemurafenib 720 mg BID. Despite discontinuation of vemurafenib, her LFTs continued to increase to grade 4 (AST=828 IU, ALT=504) 3 days later. Abdominal CT at this point showed a significant decrease in the size of her liver lesions compared to her scan 3 weeks ago. Given previous treatment with ipilimumab, an autoimmune hepatitis was suspected and prednisone 1 mg/kg was started. Immediately after starting prednisone, her LFTs started to decrease and normalized at 3 weeks after her first steroid dose. Two months after discontinuation of vemurafenib, she presented with rapidly increasing painful skin nodules. With this disease progression, vemurafenib was restarted at 720 mg BID, however, her LFTs rose rapidly within 2 weeks to grade 3 level (AST=384 IU, ALT=253 IU). Even with a short course treatment (14 days), her subcutaneous nodules showed quick shrinkage with significant pain relief. Stopping vemurafenib and starting prednisone 1 mg/kg returned her LFTs to baseline within 3 weeks. Unfortunately, 7 weeks after the second discontinuation of vemurafenib, her nodules started to increase again with moderate pain, so this time vemurafenib 480 mg BID with concurrent 20 mg prednisone was prescribed. Her LFTs increased during the first week (AST=356 IU, ALT=180 IU), again with dramatic clinical response noted in tumor shrinkage, leading us to stop vemurafenib treatment again and increase her prednisone

dose from 20 mg to 40 mg. This brought her LFTs back down (AST=60 IU, ALT=110). At her next appointment, the decision was made to start her on vemurafenib 240 mg with 40 mg of prednisone, as her melanoma had remained responsive to vemurafenib throughout her clinical course. Her tumor again showed quick response and this time the patients LFTs remained stable at a grade 1 level. Since starting this last regimen, the patient was able to wean her prednisone dose to 10 mg once a day over 4 weeks with no significant elevation of her LFTs and her disease continued to demonstrate good clinical response to vemurafenib.

Eight months from the first dose of vemurafenib, her disease progressed and she succumbed to death 2 months into this progression. Her vemurafenib dose was increased to 720 mg at progression but she did not experienced liver dysfunction with concurrent low dose prednisone. See Figure 1 for the patient's LFTs over time.

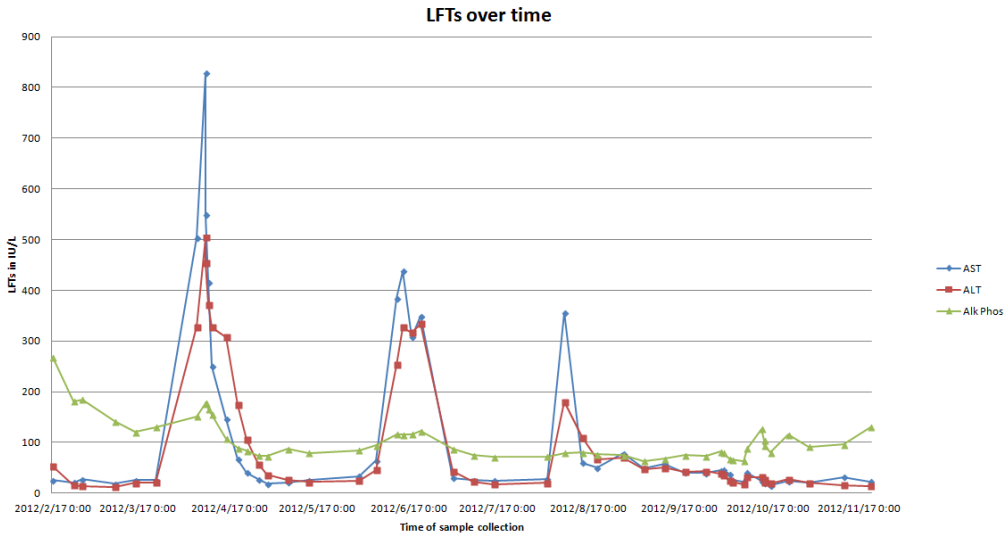

Figure 1 LFTs over time. The patient did not drink alcohol nor partake in any behaviors risky for infection during her therapy with either ipilimumab or vemurafenib. A liver biopsy was not performed due to presumed lack of clinical yield.

Discussion

Hepatitis and elevated liver function tests are common adverse events associated with medicine administration. The differential diagnosis of elevated LFTs includes viral, autoimmune, inherited metabolic disorders, endocrine disorders, ischemia, cholestatic and toxic causes. Our patient had a negative hepatitis viral panel. Liver ultrasound did not visualize significant disease progression or cholestatic processes. Other than her history of hypothyroidism, the patient did not have signs, symptoms or a history of inherited or acquired metabolic or endocrine disorders. The timing of her LFT elevations, along with the negative workup for other causes, led us to suspect an autoimmune hepatitis, likely related to her treatment with previous ipilimumab. In the case presented, the contribution of either drug to the adverse event cannot be reliably ruled out. The timing of the events suggested drug toxicity from vemurafenib as the cause of her liver dysfunction, but simple discontinuation of vemurafenib did not resolve the liver dysfunction in this case.

Immune-related adverse events associated with ipilimumab therapy have been reported

up to two years after discontinuation of therapy [1]. Both discontinuation of ipilimumab and administration of corticosteroids induce resolution of autoimmune hepatitis, with a median time to resolution of 3.1 to 4.6 weeks when treated with corticosteroids with only 1.9% of patients requiring additional immunosuppressive therapy with either infliximab or mycophenolate mofetil [2]. In this presented case the response to steroids is suggestive of a contribution from an auto-immune related adverse event. There are reports of liver dysfunction associated with imatinib, responsive to corticosteroids [3] but there is a report of steroid refractory hepatotoxicity related to treatment with gefitinib [4]. To our knowledge, there are not similar case reports involving vemurafenib in the literature.

In previously untreated patients, treatment with ipilimumab/dacarbazine combination therapy has demonstrated an increased median survival time compared to monotherapy dacarbazine monotherapy [5]. In patients previously treated, treatment with ipilimumab and gp100 vaccine has been shown to increase median survival compared to those patients only receiving the gp100 vaccine [1]. In treatment naïve patients with BRAF mutation positive metastatic melanoma, treatment with vemurafenib is associated with an increase in progression free survival over those patients treated with dacarbazine [6]. Patients with previously treated BRAF mutation positive melanoma who subsequently undergo treatment with vemurafenib demonstrate a median survival of 15.9 months in a phase 2 trial [7].

In recent ipilimumab studies, 2.1% of patients experienced elevations in their liver function tests when treated with ipilimumab and gp100 versus 3.8% of patients treated with ipilimumab alone [1]. Robert et al. report an alanine aminotransferase elevation in 29.1% of patients treated with ipilimumab and dacarbazine but an elevation in only 4.4% of patients treated with dacarbazine monotherapy [5]. The relatively low incidence of auto-immune hepatitis associated with ipilimumab monotherapy and the greatly increased incidence of autoimmune hepatitis associated with ipilimumab/dacarbazine combination therapy indicates the potential for ipilimumab combination therapy to have a greater propensity to induce autoimmune hepatitic reactions than ipilimumab monotherapy.

Vemurafenib has been associated with liver toxicity, with abnormal liver function studies occurring in 23 of 132 (17%) patients while on vemurafenib, with grade 3 and 4 reactions occurring in 8 (6%) and 4 (3%) patients respectively [7]. Generally, hepatotoxicity due to vemurafenib resolves with discontinuation of therapy [7].

Corticosteroids have become the standard treatment for immune-related adverse events (irAEs) associated with ipilimumab and their use in various irAEs was detailed by Weber in 2012 [8]. The important of corticosteroid treatment of irAEs is suggested by a case of fulminant autoimmune hepatitis resulting in death in which the administration of corticosteroids was delayed [2]. Prophylactic use of corticosteroids, however, has not been found to be efficacious in preventing ipilimumab related irAEs [9]. Recent studies indicate that treatment of ipilimumab-related irAEs with corticosteroids do not affect the efficacy of treatment with ipilimumab [10, 11]. These results demonstrate the feasibility and importance of treating through side effects associated with ipilimumab with corticosteroids in a timely manner.

Conclusion

The frequency that patients with metastatic melanoma get exposed to both ipilimumab and vemurafenib during their treatment course will likely increase, because as clinicians we want to utilize all available therapies to treat metastatic melanoma as indicated. Currently, a prospective, multicenter, phase 1-2 trial,

ClinicalTrials.gov number, NCT01400451, is investigating the safety and efficacy of concurrent therapy with ipilimumab and vemurafenib for BRAF V600E mutant metastatic melanoma. Hepatotoxicity with combination of vemurafenib and ipilimumab with this phase 1 trial was reported as a correspondence in a recent New England Journal of Medicine[12]. Practitioners should monitor patients carefully, including their liver function tests, during vemurafenib treatment in a patient who has previously been treated with ipilimumab due to the potential for liver dysfunction. While not all drug related liver toxicity has been shown to be responsive to corticosteroids, for patients previously treated with ipilimumab who experience elevated LFTs while on vemurafenib, re-challenging with a reduced dose of vemurafenib and concurrent corticosteroids treatment may be tried with the goal of maintaining good clinical efficacy and controlling liver injury.

Consent

The patient's spouse has given informed consent to the publication of this report.

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