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Case Report

Can we Restart Vemurafenib after Severe Hepatotoxicity? A Case Report

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Abstract

Advanced melanoma is a highly aggressive tumor with low response rate to the majority of cytotoxics. Currently, Vemurafenib is the treatment of choice for patients with BRAF mutant melanoma. It is generally safe and a well-tolerated drug and severe hepatotoxicity is rarely reported. This case reports our clinical experience of grade 4 hepatotoxicity related with Vemurafenib, which was successfully treated with steroids and restart of Vemurafenib under steroid therapy.

Introduction

Advanced melanoma is highly aggressive tumor with low response rate to the majority of cytotoxics. Recently molecular targeted therapies have changed the management of metastatic melanoma. Vemurafenib is the first molecularly targeted agent approved for treatment of advanced melanoma in US and Europe. Vemurafenib selectively inhibits mutated BRAF V600E kinase, therefore aberrant mitogen-activated protein kinase (MAPK) pathway signaling is reduced. BRAF V600 mutations are seen in approximately 50% of all melanomas [1]. Vemurafenib is generally safe and a well-tolerated drug, but wide spectrum of toxic effects have been described. In BRIM-3 study it was reported low incidence of National Common Toxicity Grading Criteria (NCTGC) grade 3 or 4 toxicities, however 38% of patients in vemurafenib arm required dose reduction [2]. Liver function abnormalities were recorded as 13% in vemurafenib safety study [3]. There is no specific treatment for vemurafenib-associated hepatotoxicity and in case of grade 3-4 toxicity recommendation is to stop the drug indefinitely [4]. To our knowledge, this is the first case report in the literature for restarting vemurafenib after resolving of grade 4 hepatotoxicity.

Case presentation

Fifty-four years old male admitted to hospital with black, hemorrhagic, nodular lesion on his scalp in May 2014. His physical examination revealed a hemorrhagic, ulcerated 3 cm lesion on the vertex and 2 cm fixed lymphadenopathy on right cervical region. His pathological diagnosis was malignant melanoma. Preoperative CT-scans showed no systemic metastasis except cervical lymphadenopaties. Wide tumor excision on scalp with skin greft reconstruction and bilateral neck dissection was performed on June 2014.

Histopathological examination revealed pT4N3, nodular type malignant melanoma, with Breslow thickness of 1.2 cm and Clark level 5. On July 2014 his PET-CT showed pathologically high FDG uptake in the operated region as well as new subcutaneous nodules on the right side of his neck. As he relapsed locoregionally he was assessed inoperable. He was started on vemurafenib 960 mg BID on July 2014 after BRAF-V600E mutation was detected. His liver function tests, complete blood count and other biochemical analyses were within normal limits before vemurafenib treatment. Two weeks after vemurafenib administration, patient only reported grade 1 asthenia, while his alanine transaminase (ALT) was 1083 U/L, aspartate transaminase (AST) 490 U/L, alkaline phosphatase (ALP) 124 U/L, gamma glutamyl transferase (GGT) 190 U/L, total bilirubin 1.9 mg/dl, direct bilirubin 0.58 mg/dl, prothrombin time (PT) 14.6 sec, international normalized ratio (INR) 1.22, leucocytes 13600/μL, neutrophils 6300/μL, eosinophils 3700/μL, hemoglobin 12.2 gr/dl, platelets 258.000/μL. Upon these laboratory results toxic hepatitis due to vemurafenib was suspected and the drug withheld. We further evaluated him for differential diagnosis of liver enzymes elevation. Patient denied using any drug or herbal supplements. Serology were negative for HBsAg, HBeAg AntiHbs-IgG and IgM, Anti HAV-IgM, Anti-HCV, EBV-IgM, CMV-IgM, anti-mitochondrial antibody, anti-smooth muscles antibody and anti-liver kidney microsomal antibodies. We could not detect any microbiological evidence on his stool examination or clinical sign on his physical examination for parasitic infections. After 3 days of vemurafenib discontinuation his liver enzymes were still greater than 1000 U/L. He was started on 1 mg/kg dose of methyl-prednisolone. He was followed weekly. On 20th day of methyl-prednisolone treatment ALT and AST values decreased to 209 U/L and 89 U/L, respectively. Steroid treatment was reduced to half dose afterwards. On 48th day of steroid treatment AST was 25 U/L, ALT 51 U/L, ALP 83 U/L, GGT 133 U/L, total bilirubin 1.34 mg/dl, INR 0.83, eosinophil count 200/μL. At the time we didn't have any other available treatment option for this patient and therefore we restarted vemurafenib at the dosage of 480 mg/day. Concurrently steroid dose was tapered and was stopped in a month. At the end of 6th week we managed to reach full dose of vemurafenib without any impairment in liver function tests. On the 14th day of full dose of vemurafenib, laboratory values were; AST: 36 U/L, ALT: 63 U/L, eosinophil count: 200 /μL, total bilirubin: 1.5 mg/dl, ALP: 85 U/L and GGT: 116 U/L. On the 30th day, values were; AST: 37 U/L, ALT: 48 U/L, ALP: 72 U/L, GGT: 76 U/L, total bilirubin: 1.49 mg/dl, eosinophil count: 400/μL. After 2 months of full-dose of vemurafenib disease progression was observed and the treatment was stopped.

Discussion

Liver function abnormalities accounted for 13% of adverse events recorded in vemurafenib safety study [3]. They included elevations in ALP, bilirubin, and transaminases as well as other biliary and liver impairment and only 5% of cases were graded as 3 or 4. Severe hepatotoxicity can be seen with vemurafenib as in a phase I trial combination of vemurafenib and anti-CTLA-4 antibody ipilimumab was discontinued due to hepatotoxicity [5]. Also fatal hepatotoxicity have been reported with vemurafenib when used in combination with radiotherapy [6]. Therefore, liver function tests should be monitored before initiation of treatment, after two weeks and monthly thereafter during vemurafenib treatment, or as clinically indicated. In case of grade 3-4 hepatotoxicity, it is suggested to permanently discontinue the drug. There is no any specific approach after vemurafenib hepatotoxicity other than drug discontinuation and general supportive treatment [4]. To our knowledge, this is the first case in the literature showing restarting vemurafenib and gradually increasing to full dose after resolution of vemurafenib related grade 4 hepatotoxicity. In addition steroid usage may have contributed to quick resolution of this severe hepatotoxicity. Furthermore, concurrent use of steroid with vemurafenib might have given us the opportunity to restart and to increase to full dose in one month. On the other hand, we don't know whether simultaneous usage of steroid decreases the efficacy of vemurafenib or not. High eosinophil count upfront was a suggesting finding of toxic hepatitis. Therefore, we opted to administer glucocorticoid treatment to these patient.

In conclusion, vemurafenib is a very important agent in the treatment of BRAF mutant melanoma patients. Therefore, after resolution of grade 3-4 hepatotoxicity, we think, it's a reasonable approach to restart vemurafenib with gradual dose escalations together with concurrent methyl-prednisolone treatment.

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