ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 04, pp.11319-11321, April, 2020

DOI: https://doi.org/10.24941/ijcr.37834.04.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

PAZOPANIB INDUCED HYPERAMMONEMIC ENCEPHALOPATHY IN A PATIENT WITH METASTATIC CHONDROSARCOMA

[1,*]Sondos A. Alturkistani and [2]Shadi S. Al-Khayyat and [3]Marwan R. Al-Hajeili

[1]Resident, Department of Internal Medicine, King Abdulaziz University
[2]Associate professor and consultant of oncology, Department of Internal Medicine, King Abdulaziz University
[3]Department of Medicine, King Abdulaziz University, Associate professor and consultant of Oncology

ARTICLE INFO

Article History:
Received 08th January, 2020
Received in revised form
24th February, 2020
Accepted 18th March, 2020
Published online 30th April, 2020

Key Words:
Ergonomics, Posture, Pain, Office, Heart Rate, Blood Pressure, Workload

ABSTRACT

Targeted anit-cancer drugs in general and Tyrosine Kinas inhibitors specifically have been approved and used recently; so did the understanding of their limitations and side effects. Hitherto, side effects of certain Tyrosine Kinase inhibitors are still being reported with no or little precedents. An example of these rare under reported adverse reactions is hepatic encephalopathy (HE) which has been reported for a total of 11 times with Sunitinib, Regorafenib, Sorafenib and once with Pazopanib. This is a case of a 32-year-old known case of advanced breast adenocarcinoma who underwent neoadjuvant chemotherapy followed by surgery and radiotherapy with excellent response initially but progressed unfortunately to include metastatic chondrosarcoma. Pazopanib has been offered to the patient at her late stages as part of a palliative therapy plan. Soon after, the patient presented to the ER with change in level of consciousness. After ruling out other differentials; HE has been suspected then approved when symptoms resolved after its discontinuation and proper management. The infrequent encounter of HE as a side effect of Pazopanib renders its diagnosis a challenge. This case illustrates the importance of keeping an open mind to rare diagnoses and is a valuable addition to the literature in this matter.

Citation: ***Sondos A. Alturkistani and Shadi S. Al-Khayyat and Marwan R. Al-Hajeili.*** **2020.** "Pazopanib Induced Hyperammonemic Encephalopathy in a Patient with Metastatic Chondrosarcoma", *International Journal of Current Research*, 12, (4), 11319-11321.

INTRODUCTION

Cancer medications were first used in the mid 20th century after the discovery of alkylating chemotherapeutic agents during world war. Though this breakthrough; a shortcoming of these agents was the fact that their effect was far from specific; hence they imposed troublesome systemic side effects hindering the continuation of treatment in many patients (Schwartz, 2011) Since then and through accumulative understanding of the kinetics of cell division and the molecular nature of cancer; advancements in the treatment of cancer begun to rise providing physicians not only a wider selection of chemotherapeutic drugs, but also agents that were targeted to specific faults in the cell division process, as well as: signaling pathways, oncogenes and tumor suppressor genes associated with cancer; aiming to decrease systemic side effects and toxicity of normal healthy tissue. The movement towards targeted anticancer therapy began in the 1970's when Tamoxifen was first approved for the treatment of ER+ breast cancer as a novel endocrine targeted therapy (Dy, 2013).

Corresponding author: **Sondos A. Alturkistani,**
Resident, Department of Internal Medicine, King Abdulaziz University.

Furthermore, an exponential growth of different classes of targeted chemotherapeutic agents followed. For example, an important class of Proteins named Tyrosine Kinases (PTK) were found to be essential in the regulation of cell growth, differentiation and death faults of the PTK have proven to be associated with more than 50% of oncogene products leading to proliferation disorders, tumor invasion, metastasis and chemotherapy resistance (Drake, 2014). For that reason, enormous human and financial resources have been recruited to the field of protein kinase inhibitors' research and development, with Imatinib being the first to be FDA approved in 2001. Hitherto, over 20 Tyrosine Kinase Inhibitors (TKI) targeting different receptors as: vascular endothelial growth factor receptor VEGFR, endothelial growth factor receptor EGFR, platelet derived growth factor receptor PDGFR and many more - have been developed and used either in adjunct to conventional chemotherapy or as first line treatment agents themselves (Drake, 2014). Although this advancement in cancer management, TKI brought their own limitations to the picture side effects are not uncommon in patients using TKI's; as hematologic toxicities that are commonly seen in the form of anemia, neutropenia and thrombocytopenia. While common non-hematologic adverse effects include nausea, vomiting, diarrhea, edema and hypothyroidism.

That is for most types of TKI's, while keeping in mind adverse effects specific for each class of TKI's as: dermatologic manifestations of endothelial growth factor receptor inhibitors EGFR and sub-ungal splinter hemorrhages associated with the use of agents that inhibit vascular endothelial growth factor receptor VEGFR and platelet derived growth factor receptor PDGFR (Hartmann, 2009). In general, and due to the previously mentioned limitations, many side effects of targeted anti- cancer therapies remain unanticipated and/or under-reported; which lead to discontinuation of a good number of drugs during their clinical development (Dy, 2013) An example of these rare under reported adverse reactions is hepatic encephalopathy which has been reported for a total of 12 times with Sunitinib, Regorafenib, Sorafenib and Pazopanib for 5,4,2 and 1 times respectively, between the years 2011-2016 (Kongsuphon, 2018). This study is intended to report a case where a patient that was started on Pazopanib -in addition to conventional chemotherapy regimen for metastatic chondrosarcoma -developed hyperammonemic hepatic encephalopathy, with a detailed description of her presentation, course of illness and treatment.

Case: A 32-year-old known case of locally advanced HER-2 over expressing breast cancer received - initially- 4 cycles of Cyclophosphamide and Doxorubicin followed by additional 4 cycles of Docetaxel and Trastuzumab. Excellent response was seen which qualified her for a modified radical mastectomy. Following the surgery, the patient was put on adjuvant Radiotherapy combined with Trastuzumab for a total of 13 cycles. Tamoxifen was then started immediately after the completion of radiotherapy. Eight months later erythema started to develop at the surgical site associated with multiple superficial skin ulcerations. An evaluation by her surgeon was followed by a biopsy that showed recurrent Her-2 +ve breast cancer. Restaging was done which showed limited disease to the skin, however, being it a wide field no surgical option was offered, meanwhile Kadcyla was started given that she had just completed Trastuzumab. Great response was seen as all lesions and ulcers disappeared.

Until five months later, the patient started complaining of dyspnea. A CT chest revealed a pleural effusion with a mediastinal pleural mass. Therapeutic paracentesis followed and an attempt of pleurodesis failed. The patient was sent to the OR for release of the trapped lung. Simultaneously a surgical biopsy was taken that showed chondrosarcoma. A lengthy discussion between surgeons and oncologists decoded to start the patient on Gemcitabine which she received 3 cycles of until she presented again with worsening of her dyspnea. Unfortunately, CT imaging showed progression of the disease so Pazopanib was started. Around seven weeks later, the patient presented to the emergency room complaining of severe nausea, vomiting and constipation for 7 days. Within one day, the patient was discharged on Metoclopramide, Omeprazole and Ondansetron after discontinuation of Pazopanib and was given a 3-week outpatient appointment for follow up. A couple of days later, on 19th of September the patient presented to the ER again, with non-resolving symptoms in addition to a decrease in the level of consciousness and history of subjective fever. On examination the patient was drowsy, not fully oriented, jaundiced, had temperature of 38.7 and BP of 153/64 mmHg. Heart sounds were normal, bilateral basal crepitations were auscultated. Abdomen was distended and mildly tender with no lower limb edema. Initial investigations are listed below at Table 1. Brain CT was done and ruled out the presence of an acute insult and metastasis. No white-gray matter differentiation was appreciated. After an inconclusive abdominal US; abdominal CT ruled out intestinal obstruction by visualizing patent bowel but verified the presence of direct extension of the right chest wall mass as an ill- defined lesion into lobe VIII with a rim of fluid surrounding the liver. Right sided pleural effusion and mild ascites were also seen. In regard to her lab and imaging results, the patient was admitted as a case of Pazopanib induced hyperammonemic hepatic encephalopathy. During her admission the patient was started on Lactulose 15 mg TID, Metoclopramide 10mg, Ondansetron 8mg, Omeprazole 40mg. Significant improvement of symptoms namely her level of consciousness was appreciated on the 3rd day of admission; which favored the differential of HE over the effect of liver invasion. The patient was discharged after 5 days of inpatient care in a consciousness state similar to her baseline. Re-challenging the patient using Pazopanib was not done. It is worth to mention that a few months later the patient presented with history of fever and admitted through the ER as a case of community acquired pneumonia vs. progression of the disease that unfortunately lead to her death.

DISCUSSION

As in this reported case, the TKI used was Pazopanib, a potent, selective, broad-spectrum, multi-targeted inhibitor of receptor tyrosine kinases, including VEGFR-1, 2, 3, c-kit and PDGFR. Commonly seen adverse reactions with the use of Pazopanib included rises in transaminases, diarrhea, fatigue, nausea, hair de- pigmentation, and hypertension and lead to discontinuation of drug in 5% of the patients. This case is thought to be the 12th case to report TKI induced hepatic encephalopathy (HE) and the second to report Pazopanib as the cause. In consequence to the fact that HE is an unanticipated adverse reaction of this class of drugs; the exact pathophysiology is not yet identified. One theory commonly mentioned in similar reports is the class effect of anti- VEGFR and anti-PDGFR agents that inhibit new vascular formation in many organs including brain; which interferes with the blood-brain barrier. Another hypothesis is the effect of smaller, supposedly non-toxic doses on a liver with limited reserve due to either malignant infiltration and/or the effect of reductive surgery and/or systemic chemotherapy. This patient did have some metastatic deposits in the liver but the resolution of her symptoms after discontinuation of Pazopanib excludes metastasis as the cause behind her HE. Similarly, chemotherapy induced HE is excluded due to the fact that her symptoms resolved while on the same dose of Gemcitabine and Trastuzumab. Another supporting evidence of TKI induced HE is the decreasing ammonia levels in response to the initiation of the treatment and corresponding to her clinical picture. Treatment of hyperammonimic HE remains the same regardless of the causing factor. In that logic, management will revolve around decreasing the GI tract production and absorption of ammonia.

Complete Blood Count			
Hb	12.5 g/dL	RBC	4.46 M/uL
WBC	8.07 K/uL	Platelets	34 K/uL
Urea and Electrolytes			

Table 1. Laboratory results

Urea	4.8 mmol/L		Sodium - Na	131 mmol/L
Creatinine	65 umol/L		Potasium - K	3.6 mmol/L
Phosphate	94 mmol/L		Calcium - Ca	1.8 mmol/L
Liver Function Test, Ammonia and Lactic Acid				
ALP	257 U/L		AST	144 U/L
ALT	84 U/L		GGT	22 U/L
Total Bilirubin	40 umol/L			
Ammonia	20/9/2018	147 mmol/L	Lactic Acid	4 mmol/L
	22/9/2018	87 mmol/L		
Arterial Blood Gases				
pH			7.47	
PCo2	20 mmHg		HCO3	18.5 mmol/L

Lactulose continues to be the mainstay management in these cases; acting as a non- absorbable disaccharide alkalizing colonic medium causing subsequent ammonium trapping and promoting non– urase-producing bacteria with mass removal of colonic bacteria through catharsis (Bajaj, 2010). It is worth to mention that low protein diets have shown not to be safe in such cases due to their activation of the starvation physiology which may worsen the outcome (Córdoba et al., 2004; Kachaamy, 2011) As a final option, hemodialysis is reserved for patients with refractory to medical management. Seven out of the 12 previously reported cases have been treated successfully with Lactulose. Two have been treated by branched chain amino acids and 2 via antibiotics, not to mention that discontinuation of the causative agent was established in all 12 alongside treating medications; and once, alone. Re-challenging patients with the same agent has been carried out in 3 of the 12 cases; with unfavorable outcomes. For all three-patient's recurrence of HE was induced; whether half or full dose was administered. (Kongsuphon, 2018). Finally, since HE remains an unanticipated side effect for this class of drugs, physicians are highly encouraged to acknowledge the HE potential of targeted anticancer therapy namely TKI's. Early identification and correct differentiation form other common cause of HE in cancer patients as liver infiltration, systemic chemotherapy, reactivation of hepatitis, and portosystemic shunting is vital for effective management.

REFERENCES

Bajaj, J. S. 2010. The modern management of hepatic encephalopathy. *Alimentary pharmacology & therapeutics*, *31*(5), 537-547.

Córdoba, J., López-Hellín, J., Planas, M., Sabín, P., Sanpedro, F., Castro, F., & Guardia, J. 2004. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *Journal of hepatology*, *41*(1), 38-43.

Drake, J. M., Lee, J. K., & Witte, O. N. 2014. Clinical targeting of mutated and wild- type protein tyrosine kinases in cancer. *Molecular and cellular biology*, *34*(10), 1722- 1732.

Dy, G. K., & Adjei, A. A. 2013. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: a cancer journal for clinicians*, *63*(4), 249-279.

Dy, G. K., & Adjei, A. A. 2013. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: a cancer journal for clinicians*, *63*(4), 249-279.

Evolution of Cancer Treatments: Chemotherapy." *American Cancer Society*, Cancer.org, 12 June 2014, www.cancer.org/cancer/cancer-basics/history-of-cancer/cancer-treatment-chemo.html.

Hartmann, J. T., Haap, M., Kopp, H. G., & Lipp, H. P. 2009. Tyrosine kinase inhibitors-a review on pharmacology, metabolism and side effects. *Current drug metabolism*, *10*(5), 470-481.

Jiang, Q., Jiang, X. H., Zheng, M. H., Jiang, L. M., Chen, Y. P., & Wang, L. 2008. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *European journal of gastroenterology & hepatology*, *20*(11), 1064-1070.

Kachaamy, T., & Bajaj, J. S. 2011. Diet and cognition in chronic liver disease. *Current opinion in gastroenterology*, *27*(2), 174-179.

Kongsuphon, N., Soukavanitch, M., Teeraaumpornpunt, N., Konmun, J., Ativitavas, T., & Ngamphaiboon, N. 2018. Multi-Targeted Tyrosine Kinase Inhibitor-Induced Hyperammonemic Encephalopathy: a Report of Two Cases Using Pazopanib, Sunitinib, and Regorafenib. *Journal of gastrointestinal cancer*, 1-3.

Schwartz, R. 2011. The Emperor of All Maladies—The Beginning of the Beginning. *New England Journal of Medicine*, *365*(25), 2353-2355.

Willson, K. J., Nott, L. M., Broadbridge, V. T., & Price, T. 2013. Hepatic encephalopathy associated with cancer or anticancer therapy. *Gastrointestinal cancer research: GCR*, *6*(1), 11.

****