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Case Report

A Rare Case of Gemcitabine-Induced Thrombotic Microangiopathy (TMA) in the treatment of Metastatic Nasopharyngeal Carcinoma, presenting to Nephrology Division Khyber Teaching Hospital, Peshawar

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Abstract

Abstract: Platinum-based concomitant chemo radiotherapy is considered the standard therapy in patients with advanced nasopharyngeal carcinoma worldwide. Gemcitabine, a nucleoside analogue of cytarabine primarily authorized in 1996 for the cure of unrespectable pancreatic carcinoma. Gemcitabine causes endothelial injury directly and therefore may lead to thrombotic microangiopathy in cancer population.

Key words: Gemcitabine(GEM), Nasopharyngeal carcinoma(NPC), Thrombotic Microangiopathy (TMA), Gemcitabine-induced thrombotic microangiopathy (GiTMA)

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy of head and neck region having diverse occurrence all over the world.[1] About 5% to 11% nasopharyngeal cancers are metastatic while 15% to 30% will showed recurrence or dissemination after chemotherapy, incompatible for radio surgical intervention.[2] Therefore, the most important management routes for patients with frequent or metastatic nasopharyngeal carcinomas are palliative rehabilitations.

Presently, there is not any constant regime used for induction chemotherapy of nasopharyngeal carcinoma, However the combination of fluorouracil (FU) with platinum or gemcitabine (GEM) is extensively in practice.[3] Gemcitabine, a nucleotide analogue yielding chemotherapeutic effects by inhibiting DNA synthesis, involved in multiple gastrointestinal and lung malignancies. Meta-analysis revealed that GEM play vital role in management of nasopharyngeal carcinoma with significant beneficial outcome and can tolerate side effects.[4]

Gemcitabine-induced thrombotic microangiopathy (GiTMA) is an unusual, lethal condition of unrestrained complement activation, characterized by hemolysis, thrombocytopenia, and acute renal failure. GiTMA signifies one subdivision of microangiopathic maladies distinctive from atypical hemolytic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP).

Case report

A 54 -year-old patient previously no co-morbidities working as driver in Dubai for last 4 years presenting to medical OPD with shortness of breath, dizziness, headache and neck swelling for 3 months. The general physical examination revealed pallor, cachectic axillary and cervical lymphadenopathy with marked weight loss. The lymph node biopsy was advised which showed metastatic poorly differentiated squamous cell carcinoma. In addition, the MRI spine showed compression collapse of L1 and L2 vertebrae suggesting metastatic lesions. Furthermore, whole body bone scan was recommended suggesting increased tracer uptake in the frontal skull bone, ribs, sternum, vertebrae and trochanteric region of femur. The patient did multiple visits to oncologist who commenced him on injectable chemotherapeutic agents i.e. Gemcitabine and carboplatin with doses of 1400mg and 450mg of 4 cycles each respectively. During second session of chemotherapy the patient renal functions deteriorated slowly along with bone marrow dep-

ression showing pancytopenia. Therefore, he was commenced on injectable filgrastim along with oral dexamethasone. The patient was referred to Nephrology OPD where further workup was done showing increased urea-creatinine levels, cytopenias, hyperlactatemia and transaminitis. In addition to that the peripheral smear showed anisocytosis, fragmented red blood cells with increased reticulocyte count. After all, the thrombotic microangiopathy(TMA) diagnosis was made. Meanwhile the gemcitabine was withdrawn, 3 sessions of plasma exchange followed by 2 session of hemodialysis was done along three doses of methylprednisolone. The patient was counselled about the disease prognosis and adverse effects of chemotherapeutic agents. The laboratory investigations done throughout his treatment are given in tabulated form.

Discussion

Nasopharyngeal carcinoma (NPC) is an uncommon malignancy in North America comparative to endemic zones like Southeast Asia, North Africa, and the Mediterranean. The prevalence of NPC amongst Caucasians is 0.2/100,000 linked with 15–50/100,000 in Southern China.[5] Thrombotic microangiopathy(TMA) is a microvascular malady described by platelet thrombosis and damage to glomerular endothelium. The precise pathogenesis of GiTMA is yet uncertain, but it is proposed that damages to renal glomerular endothelium is primary defect. GiTMA is a sporadic, severe condition with frequency and mortality extending from 0.015% to 1.4%[6] and 50% to 90% respectively.[7]

TMA has three main components (1) microangiopathic hemolytic anemia (MAHA), (2 thrombocytopenia (decreased platelets count) and (3) organ injury (acute kidney insult). The model of TMA commonly comprises TTP, STEC-HUS, aHUS, and secondary TMA.[8] Secondary TMA has been linked with a variability of causes, comprising microbial and biological infections, medications, cancers, motherhood, and systemic illnesses. Anti-cancers agents leading to secondary TMA are mitomycin C, cisplatin, and Gemcitabine. The current patient had an advanced nasopharyngeal carcinoma cured with GEM, harmonious with secondary TMA.

Up till now, the wide-ranging pathophysiology of drug induced TMA is unclear, however prostaglandins diminished the von Willebrand factor(VWF) production, followed by endothelium injury and ultimately platelets coagulation. TMA is usually evoked within 5 to 8 months after treatment. The most common feature described in our patient after gemcitabine treatment of TMA is de novo hypertension.9 Gemcitabine-induced TMA is treated by its cessation, hemodialysis, plasmapheresis and anti-hypertensive drugs. GiTMA can occur after

Table 1: *Lab Investigations of Patient*

DATE OF TESTS	Reference Ranges	02-06-2023	26-06-2023	12-10-2023	19-10-2023	21-10-2023
Leucocytes Count (10.e3/uL)	4-11	7	2.9	8	23	10
Hemoglobin (g/dl)	12-17	13	6	9	8	7
Platelets (10.e3/uL)	150-450	250	71	133	117	90
Lactate Dehydrogenase (U/L)	91-180	-	1456	1092	-	495
Creatinine (mg/dL)	0.6-1.2	4	6	5	6	5
Urea (mg/dL)	10-50	92	103	74	80	72
Alanine Transaminase (ALT)	10-50	103	404	305	-	80
Peripheral Smear (RBC Morphology) with Retic count(%)	-	-	-	Bicytopenia Anisocytosis ++ Hypochromic Cells ++ Fragmented Cells + Retic count 11%	-	-
Uric Acid (mg/dL) (excluding Tumor lysis syndrome)	3.4-7	6.4	-	7.4	-	-
Urine R/E	-	Protein- Trace Rest- Unremarkable	-	Protein- + Rest -Unremarkable	-	-
Sodium (mmol/L)	135-145	131	-	122	132	139
Potassium (mmol/L)	3.5-5.1	4	-	3.4	3.5	3.9
Serum Calcium (mg/dL)	8-10	8.5	-	8	-	8.55
24 Hours Urinary Proteins (mg/24 hours)	<150	-	-	1541/1300ml	1125/2 500ml	392/800 ml

an accumulative dosage of 2450 mg/m^2 has been introduced, but the hazard of rate rises when the increasing dose overtunes 20000 mg/m^2.[10]

A study conducted on nasopharyngeal carcinoma patients by Leung and colleagues showed GEM unaided (dose 1250 mg/m^2 on Days 1 and 8 every 21 days) attained a cure rate of 28% in chemotherapy-naive cases versus 48% cure rate among formerly treated cases.[11] Meanwhile Ngan et al revealed (gemcitabine dose of 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin dose of 50 mg/m^2 on Days 1 and 8 every 28 days) attained a remarkable response rate of 77%.[12]

Withdrawal of gemcitabine is the primary step in management. Majority cases presenting with thrombocytopenia and microangiopathy are frequently cured with plasma exchange in TTP till ADAMTS[13] report. Stoppage of gemcitabine, Steroids, plasmapheresis, filgrastim to raise the cell counts followed by hemodialysis are the treatment sequence remedies in our patient.

Conclusion

In conclusion, we report an uncommon unfriendly experience of gemcitabine-induced TMA in a patient with advanced nasopharyngeal carcinoma. Gemcitabine-induced TMA is comparatively exceptional, and nearby has been no well-known cure. It is tremendously essential to withdraw gemcitabine in the initial phases of TMA onset in a medical venue. Early diagnosis of drug-induced toxicity and TMA is essential for accurate metastatic cancer treatment in the forms of plasma exchange and hemodialysis under supervision of nephrologist and oncologist.

Conflict of Interest: *None*

Funding Source: *None*

References

1. Chen YP, Chan ATC, Le QT. Nasopharyngeal carcinoma. Lancet. 2019;394(3):64-80.
2. Lee AW, Ma BB, Ng WT. Management of nasopharyngeal carcinoma: Current practice and future perspective. J Clin Oncol. 2015;33(10):3356-64.
3. Munch S, Pigorsch SU, Devecka M. Comparison of definite chemoradiation therapy with carboplatin/ paclitaxel or cisplatin/5-fluoruracil in patients with squamous cell carcinoma of the esophagus. Radiat Oncol. 2018;13(1):139.
4. Zhang L, Huang Y, Hong S. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2016; 388 (10054):1883-92.
5. Fandi A, Atum M, Azli N, Armand JP, Cvitkovic E. Nasopharyngeal cancer: epidemiology, staging, and treatment. Semin Oncol. 1994; 21(3): 382-97
6. Fung MC, Storniolo AM, Nguyen B, Arning M, Brookfield W, Vigil J. A review of hemolytic uremic syndrome in patients treated with gemcitabine therapy. Cancer. 1999;85(10):2023–32.
7. Krishnappa V, Gupta M, Shah H. The use of eculizumab in gemcitabine induced thrombotic microangiopathy. BMC Nephrol. 2018;19(1):9.
8. Jokiranta TS. HUS and atypical HUS. J Am Soc Hematol. 2017;129(10):2847-56.
9. Humphreys BD, Sharman JP, Henderson JM. Gemcitabine-associated thrombotic microangiopathy. Cancer 2004; 100(8): 2664-70.
10. Gemcitabine-associated thrombotic thrombocytopenic purpura. Zupancic M, Shah PC, Shah-Khan F. Lancet Oncol. 2007;8(3):634-41.
11. Leong SS, Foo K, Ang P, et al. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. Ann Oncol. 2002; 13(2): 150-6.
12. Ngan RK, Yiu HH, Lau WH, et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. Ann Oncol. 2002; 13(6): 1252-8.