ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 06 | June - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HIGH DOSE CYTARABINE – A CURSE FOR ACUTE BRAIN SYNDROME

Pharmacology

Dr.Vikas P.V* Clinical Pharmacist, Aster Medcity Kochi. *Corresponding Author
Dr. Amala T.A Clinical Pharmacist, Aster Medcity Kochi.

KEYWORDS

INTRODUCTION

Cytarabine is a antimetabolite, antineoplastic agent frequently using for different forms of neoplastic conditions such as AML remission induction, AML induction, AML consolidation, AML salvage treatment, APL induction, consolidation, ALL, CLL, primary CNS lymphoma, Hodgkin and non Hodkin lymphoma, meningeal leukemia etc.This pyrimidine analog exerts its antimetabolite action by aracytidine triphosphate, its active metabolite developed after entry into the cell cytoplasm [(1).] The aracytidine triphosphate decreases the DNA synthesis and repair by the inhibition of DNA polymerase. The degree of activity correlates with the incorporation into the DNA and it is responsible for the drug activity as well as the cell toxicity. Cytarabine blocks progression from G1 to the S phase, thus act specifically in the S phase of the cell cycle [(2).]

Based on 2016 WHO classification of lymphomas included two new categories of Diffuse large B cell lymphomas (DLBCL) based on their gene expression profile. They are high grade B cell lymphoma commonly referred to as double hit (DHL) or triple hit lymphomas with gene rearrangements and another broad class with high expression on immunohistochemistry but lack of gene rearrangements termed as double expresser lymphomas (DEL). R-CHOP is still the existing standard treatment for DLBCL[(3).] But the RCHOP is found to be inadequate for the treatment of DLBCL due to either primary refractoriness or relapse after the complete remission, for its subtypes DHL and DEL too. So in RCHOP failed cases intensive induction regimen is required to improve relapse free survival [(4).]

Cytarabine is one of the anticancer drugs in the intensive drug in R-Hyper CVAD/MA, R-CODOX-M/IV-AC or DAEPOCH-R etc. The IV (Intravenous) cytarabine has neurological malfunctions in the normal and intensive doses. In the following case we representing a patient had a Cerebellar ataxia injury after cytarabine administration for DEL with DHAP regimen.

CASE REPORT

A 59 year old gentleman admitted with complaints of progressive swelling of the armpit and weight loss for a year. On preliminary evaluation found that the patients have B cell lymphoma symptoms and generalised lymphadenopathy. He underwent a True cut biopsy from the left inguinal lymph node. It was suggestive of a non-Hodgkin lymphoma. PET Ct scan showed both supra and infra diaphragmatic disease and based on the radiological classification this case was fall into Ann Arbor stage IV. Later underwent detailed Left axillary lymph node biopsy and it revealed that patient have (high grade B cell lymphoma- double expresser lymphoma.

Prior to the initiation of chemotherapy patient had an ECOG(Eastern Cooperative Oncology Group (ECOG) performance status of 1, PT/INR 15.4/1.08, TLC 5.2 k/ul, Neutrophil 67.6 %, add the rest of the details.

Total Leukocyte Count (TLC) 5.2 K/ul 4.0 - 10.0, Neutrophils 67.6 % , Lymphocytes 20.3 % , Monocytes 9.7 % , Eosinophils 2.3 % , Basophils 0.1, RBC Count (Red Blood cell) L 4.21 10^{12}/ L, Haemoglobin Estimation (Hb)10.8 gm/dl, PCV (Haematocrit) L 33.9 % , MCV L 80.5 fL , MCH L 25.6 Pg , MCHC 31.9 gm/dl , RDW 13.5 % , NRBC 0.0 nRBC/100WBC, Platelet Count 167 K/uL.

Chemo : 1

Based on the initial PET CT report of stage IV metabolically active primary lymphoma, chemotherapy were started with Methotrexate 375mg/sq.m and Bendamustine 90 mg/sq.m. in first and second day. The each chemo cycle was with 28 days interval apart. Patient underwent CT chest and abdomen for interim assessment which showed good response to chemotherapy Patient was successfully completed the six cycles of initial chemotherapeutic regimen with a span of four month without any complication.

After six month of evaluation patient status was FL Gr 1 St4 b upfront Post 6 RB PET CR LDH- 431 CBC ESR- N No P \ LNE Weight gain +, LDH- 431, Weight gain +, abdominal pain, repeat CT shown significant increase in size of the mesenteric nodal mass noted and its indicating progressiveness of the disease. The unfaithful results are multiple newly FDG- avid supra diaphragmatic lymph nodes (bilateral level ii, iii, iv /supraclavicular lymph nodes) along with FDG avid large hypodense lesion with peripheral enhancement and lobulated margins in the mesentery in the umbilical region -metabolically active relapse of non-Hodgkin's lymphoma in this clinical setting (DEAUVILLE 5). FDG avid bulky lateral limb of left adrenal gland and body of right adrenal gland, metabolically active suspected adrenal lymphomatous deposit, (DEAUVILLE 5). CT detected few new tiny mesenteric lymph nodes as well as previously seen small aortocaval and para aortic lymph are FDG non avid. The disease progression leads to undergo Wedge biopsy of nodal mass at the root of small bowel mesentery shown high grade, Non-Hodgkin's Lymphoma, morphology and immuno profile consistent with high grade B-cell lymphoma, double expressor lymphoma (BCl2, BCL6 & c-myc coexpression).

IHC :The sheets of atypical lymphoid cells express diffuse strong CD79a,,CD10, BCL2, BCL6, C-myc in >40% cells, nuclear p53. These cells are negative for CD3, CD5, CD20, CD30, MUM1, cyclinD1, TdT. The background small lymphoid cells show CD3 and CD5 positive T cells. Ki-67 proliferation index is 80%.

Chemo section II

Patient had relapse after eight month of last Methotrexate and Bendamustine regimen and evaluated by PET CT and biopsy reports. The worse prognosis pushed the therapy to initiate DA R EPOCH – Level 1. Rituximab 375mg/sq.m, Etoposide 50 mg/sq.m., Inj. Adriamycin 10 mg/sq.m/day, Inj. Vincristin 0.4mg/sq.m, Inj. Cyclophosphamide 750 mg/Sq.m/, Tab. Prednisolone 60 mg with 21 period apart cycle. After 1 month Level 2 of the DA R EPOCH started with Inj. Rituximab 670mg (Day 1), Inj. Etoposide 100mg (Day 1-4), Inj. Adriamycin 22 mg(Day 1-4), Inj. Vincristine 0.7mg (Day 1-4), Inj. Cyclophosphamide 1335mg (Day 5), Tab. Prednisolone 100 mg (day 1-5), IT Methotrexate 12 mg, Cap. Arecap 125 mg - 80 mg.

After four month of DA R EPOCH therapy review CT and USG neck shown PET CT was done on shows When compared to previous FDG PET persistence of previously reported FDG avid bilateral cervical and right supraclavicular nodes now showing increase in size and number along with multiple new FDG avid supra and infra diaphragmatic lymph nodes. Metabolically active disease progression of primary NHL. Previously FDG non avid mesenteric soft tissue mass shows mild increase in size but remains FDG non avid -Metabolically quiescent lymphomatous deposit. Diffusely FDG avid bulky bilateral pharyngeal tonsils. Metabolically active lymphomatous involvement in this clinical setting. Newly FDG avid circumferential wall thickening involving terminal ileum and caecum with few newly FDG avid multiple soft tissue masses medial to caecum.

Chemo section III

PET CT findings are suggestive of disease progression leads to salvage chemotherapy (DHAP regimen) followed by autologus stem cell transplant.

Failure of the usual regimen compelled to initiate DHAP after 8 month of last chemo regimen. Dexamethasone 40 MG for four 4 days, Cisplatin 100 Mg.Sq, Cytosine Arabinoside 2gm/Sq.M.

After two weeks of the cycle one of DHAP, Patient was presented with sub-acute onset of fluctuating dysarthria, instability while walking, and incoordination of movements.

On general examination, slurring of speech, cerebellar sign and ataxia along with nystagmus positive on laboratory examination CSF protein of patient was 81mg/dl(15-45), CSF albumin was 6.5 mg/dl(10-30). On CT brain, increase in size and number of bilateral axillary and deep pectoral nodes also there is increase in number of mediastinal nodes along with cytological dissociation. The patient was treated with IV immunoglobulin 140mg at a dose of 2mg/kg for 5 days and the patient had a gradual improvement. The patient is suspected to have Cytarabine induced Cerebellar ataxia.

Later the patient status was improved and re-initiated the chemo regimen with Rituximab 375mg /m^2, Oxaliplatin 100mg/m^2, Gemcitabine 1000mg/m^2 twice a week. With modified regimen patient had no neurological complications and concluding that the reactions is induced by the cytarabine.

DISCUSSION

Mechanism of cerebellar toxicity to be inhibition of cytarabine dependent neutrophilic signals in brain. The incidence of cerebellar toxicity with high dose arabinoside cytarabine (HIDAC) is 10%[5]. Both cytarabine and its metabolites lead to neurotoxicity by a DNA synthesis-independent process since adult neurons are postmitotic [6].

The direct toxic effects of cytarabine on axonal and myelin metabolism of peripheral nerves assumed to be the cause of peripheral neuropathy, but some of them suggested vascultis is the cause [7].

The unremarkable cortical pathology confirmed that syndrome is reversible. The cerebellum was spared radiographically despite pronounced symptom and a loss of purkinje cells with reactive gliosis-the typical pathologic findings in high dose cytosine arabinoside related cerebellar injury [6].

The half-life of cytarabine in the CSF is about 2h but it will be longer if patient have renal insufficiency. Renal insufficiency has been reported as a major risk factor for cytarabine neurotoxicity in several reports [4,8,10].

Patient age (greater than 50years) appears to be the most important risk factor, both drug dose/schedule, cumulative drug disease, renal cord hepatic dysfunction and concomitant use of neurotropic antiemetic agent may also influence the risk of neurotoxicity.

In some studies like Jolson et al; they highlighted certain risk factors for the high dose cytarabine-induced cerebellar toxicity such as age greater than 50years, Total dose is 20mg/m^2, type of leukemia, disease stage, severe hyperbilirubinemia, abnormal pretreatment liver fraction and decreased creatinine clearance [7,9].

CONCLUSION

A better understanding of the pathophysiology and pharmacology of cytarabine induced neuronal injury /toxicity will allow this drug to be used for greater efficacy. Possible neurological abnormalities should be evaluated or educated to the patient for the early identification and initiation of the treatment modalities.

Abbreviations:

AML: Acute Myeloblasic leuckemia
APL: Acute Promyelocytic Leukemia
CNS: Central Nervous System
CSF : Cerebrospinal fluid
CLL: Chronic lymphocytic leukemia
R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin hydrochloride, Vincristine, Prednisolone
CVAD/MA:Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone/Methotrexate and Cytarabine
R-CODOX-M/IV-AC:Cyclophosphamide, Vincristine, Doxorubicin, High-dose Methotrexate / Ifosfamide, Etoposide, High-dose Cytarabine
DAEPOCH-R:Etoposide, Doxorubicin, and Cyclophosphamide with Vincristine, Prednisone, and Rituximab

REFERENCES

1. Uptodate
2. Cytarabine | C9H13N3O5 – PubChem
3. Steven H, Elia C, Stefano K et al.Th e 2016 version of the world health organization classification of lymphoid neoplasms; ASH publications,Blood. 2016; 127(20):2375-2390.
4. Patrick M, Andrew D. Current treatment of double hit and double expressor lymphoma;Hematology Am Soc Hematol Educ Program. 2017(1):295-297.
5. Sainz.S, Jimenz.A, Felipe.A. Cerebellar toxicity due to cytarabine: A series of 4 case; Neurologia. 2016:Vol 31, issue 7, 491-492.
6. TL Wallace, EM Johnson. Cytosine arabinoside kills post mitotic neurons:Evidence that deoxycytidine may have a role in neuronal survival that is independent of DNA synthesis. Journal of neuroscience.1989,9(1) 115 -124.
7. Martin D, Wallace T, Johnson E. Cytosine arabinoside kills postmitotic neurons in a fashion resembling trophic factor deprivation: evidence that a deoxycytidine-dependent process may be required for nerve growth factor signal transduction. J Neurosci. 1990;10:184–193.
8. Yeshurun M, Marsot Dupuch K. Acute cerebellar syndrome following intermediate-dose cytarabine. Br J Haematol. 2001;113:846.
9. Phu Ngoc Tran, Xiao-Tang Kong. Cytarabine induced acute cerebellar syndrome during hyper- CVAD treatment for B-cell acute lymphoblastic leukemia. Case Rep Neurol.2017 Jan-Apr;9(1):114-120.
10. Hasle H. Cerebellar toxicity during cytarabine therapy associated with renal insufficiency. Cancer Chemother Pharmacol. 1990;27:76–78.