ORIGINAL RESEARCH PAPER

Volume-6 | Issue-10 | October-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MORPHOLOGICAL CHANGES IN BLOOD AND BONE MARROW OF PATIENTS ON CHEMOTHERAPY FOR CANCERS

Pathology

Dr. S. Rohini Priya Assistant Professor of Pathology, Department of Pathology, Stanley Medical College.

***Dr.K.Shantaraman** Professor of Pathology and Head of the Department, Department of Pathology, Tirunelveli Medical College. *Corresponding Author

ABSTRACT

Chemotherapy is one of the important modality to combat cancer in this era. The haematological changes that occur in cancer patients receiving chemotherapy is analysed in this study. Peripheral smear and bone marrow aspiration study was done in total of 82 cancer patients receiving different chemotherapy regime. The major haematological change observed was grade I-II anemia in 49% and grade III-IV in 13.4% of the cases. Bone marrow aspiration study revealed micronormoblastic maturation in 50%, both micro and macronormoblastic maturation in 18%, megaloblastic change in 18% and 12% showed megakaryocyte hyperplasia with few dysmegakaryopoietic cells.

KEYWORDS

Cancer Chemotherapy, Haematological parameters, Bone marrow aspiration study

Introduction:

Cancer is a dreadful disease which threatens mankind. In the civil war against cancer surgical knife, radioactive rays and chemicals are used. These chemotherapeutic drugs while killing the cancer cells sometimes affect the normal cells causing minimal collateral damage. Today long term survival is possible for many patients however one in nine patients develop new cancer within fifteen years[1]. A chemotherapy regimen is combination of drugs given over a period of time. The primary treatment outcome is to eradicate and maintain the eradication of all abnormal cells in the bone marrow. This is done despite the known risks associated with these regimens [2]. Development of anemia, neutropenia, and thrombocytopenia are their associated side-effects (e.g., fatigue, infection, and bleeding)which occurs immediately while long term it has significant effect over bone marrow causing therapy related myelodysplastic changes, and carries a risk of second cancer over a period of years [3].

We aim to analyse the basic haematological parameters in patients on different chemotherapy drug regime and to correlate these morphological alterations of bone marrow aspirates.

MATERIALS AND METHOD:

This prospective study was conducted in the Department of Pathology, Tirunelveli Medical College & Hospital under due approvals of the Tirunelveli Medical College Institutional Research Ethics Committee. Patients were sourced from the Departments of General Surgery, Oncology over a period of two years from September 2011-September 2013.

Inclusion criteria included patient receiving chemotherapy for cancer at our hospital, patients receiving chemotherapy for no other related disease, Patients who are clinically stable, on written consent. Exclusion criteria included terminally ill patients, those with other medical or surgical disorder, those who receive other modes of anticancer therapy.

The Blood and Bone marrow samples were examined and the findings were recorded in a standard format .

OBSERVATION AND RESULTS :

Fig.1: Grade Of Anemia Among Patients On Chemotherapy

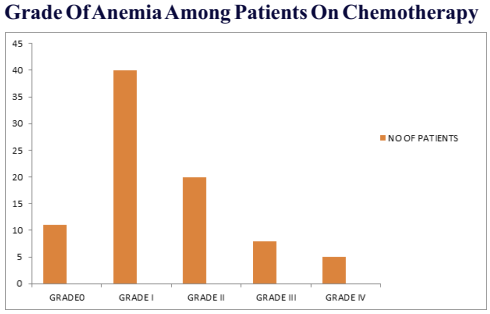


Table: 1- Anaemia observed in each regime

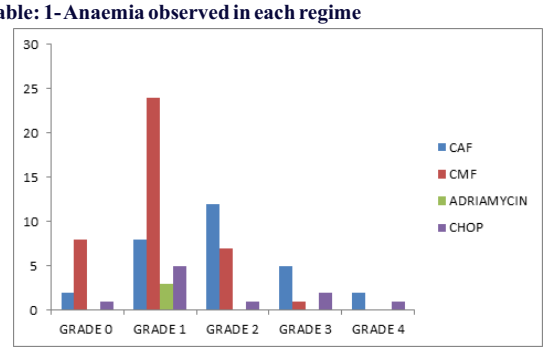


Table: 3 -Peripheral Smear Findings

RBC	Normal study-11	Microcytic hypochromic anemia -71	Macrocytic anemia-Nil
WBC	Normal-73	Leukemia-1	Leucopenia-8
Platelets	Normal-75	Thrombocytosis-2	Thrombocytopenia-5

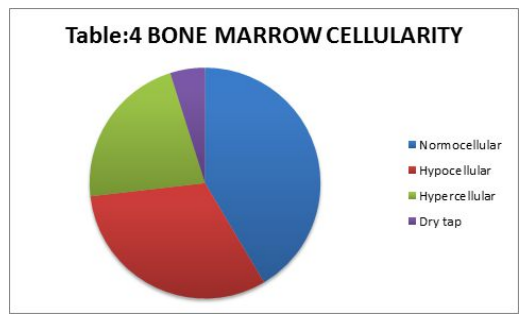


Table :5 -Bone Marrow Aspiration study

IMPRESSION	No of cases	%
Reactive erythroid hyperplasia with micro normo blastic maturation	41	50
Reactive erythroid hyperplasia with micro and macro normoblastic maturation	15	18.2
Reactive erythroid hyperplasia with megaloblastic change	12	14.6
Reactive erythroid hyperplasia with megakaryocyte hyperplasia	10	12.1

DISCUSSION:

Out of 82 cases, 29 were patients with gastrointestinal malignancies on Cyclophosphamide, Adriamycin, 5 Flurouracil (CAF),40 with breast cancer on Cyclophosphamide, Methotrexate ,5 Flurouracil(CMF),10 with lymphoid malignancies on Cyclophosphamide, Adriam ycin,Vincristine, Prednisalone(CHOP), 3 with soft tissue tumors with Adriamycin.

Overall severity of anaemia was evaluated, 11 patients showed grade 0; 40 of them showed Grade I , 20 Grade II anemia ,8showed Grade III Anaemia, 3showed Grade I V anemia. Fig[1].

In our patients receiving cyclophasphomide, Doxarubicin ,5FU reg ime ,69% showed GI to GII Anaemia; 24% showed Grade III to Grade IV Anaemia and 7% showed Grade 0 (No Anaemia). Table [1] This study results were similar to that of the percentage seen in review article by Jerome Groopman[4], in which majority of them produced grade 1 or 2 anemia (55%) and grade 3 or 4 anemia in 11% of patients receiving chemotherapy for breast cancer.

Bhavik D.Doshi et al have reported neutropenia in 51% of patients who were treated for Lymphoma & solid maliganancy[5]. Abdul Barsan et al has observed cyclophosphamide 5FU – epirubicin causing neutropenia in 40.2% of the cases receiving chemotherapy for breast cases. In our study 8 of the cases showed neutropenia[6].

This is because, it is very difficult to study the myelotoxicity caused by chemotherapeutic drugs as there are used in heterogenous combination regime. More over the time interval given in between the cycles allow the bone morrow to recover adequately. Many studies say that leucocyte nadir developed during the chemotherapy would increase DDFS and OS .10% survival advantage over others.

L mackall et al have studied the effect of intense chemotherapeutic regimes on peripheral blood counts. They have found that neutrophils, monocytes and platelets though suffered a decline during the therapy they recovered to pre treatment levels after sequential cycles, but lymphocytes didn't recover. This might be a cause for the opportunistic infections that follow intense chemotherapy[7].In a retrospective study Henry et al found neutropenia associated hospitalization in 8.7% of NHL patients ,4.2% of breast cancer patients ,3.9% of lung cancer patients. They have also found association between increased age and risk of hospitalization stronger in NHL patients[8].

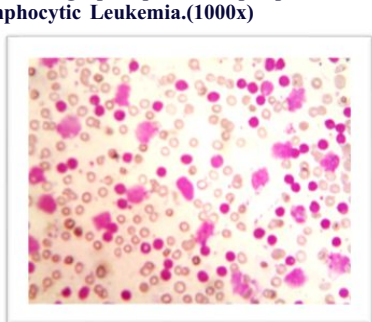
Studies have also been going on about myelotoxicity as a prognostic indicator in patients treated with chemotherapy for cancer. Anemia which develops after chemotherapy is related to tumour hypoxia which is inturn related to tumourogenic process such as proliferation and angiogenesis. Here myelotoxicity refers to Grade III-IV anaemia developed at least once while the patient is receiving chemotherapy.

When we look in to chemotherapy related thrombocytopenia, we observed mild thrombocytopenia in 3 of patients. Mitchell S Cairo in his review article says the proliferating platelet precursors are affected by chemotherapeutic agents than the mature platelets[9]. With cell cycle specific chemotherapeutic agents the megakaryocytic suppression and recovery occurs rapidly. While cell cycle non specific agents suppression occurs in a gradual manner but it is more persistent. In our study cell cycle specific agents were studied in majority.

Bone marrow aspiration study:

Changes in marrow following chemotherapy is incompletely studied in humans due to complex cell kinetics of bone marrow and different combination chemotherapy regime.Out of 82 cases 32% showed Hypocellularity, 5% dry tap .A case of Non Hodgkins Lymphoma treated with CHOP regime developed Chronic Lymphocytic Leukemia during his 5th cycle of chemotherapy. CLL was diagnosed in our peripheral smear study Fig [2].Bone marrow aspiration was attempted twice, it was dry tap. As dry tap also indicates bone marrow fibrosis this cannot be overlooked.

Fig[2]:Photomicrographic picture of peripheral smear showing chronic lymphocytic Leukemia.(1000x)



Adelstein J David et al[10] has observed dramatic increased in M:Eratio following chemotherapy. Similar to his observation we found reactive erythroid hyperplasia with micro normoblastic maturation in 50% of patients,18.29% of the bone marrow smears revealed reactive erythroid hyperplasia with micro & macronomoblastic maturation .He also observed megaloblastic maturation as common abnormality following methotrexate and 5 Fluorouracil. Similarly Out of 82cases 14.6% showed megaloblastic change in marrow. Monica Jain has reported a case of showing transient abnormal megakaryocytic hyperplasia secondary to All trans retinoic acid therapy[11].Thiele Jnergen et al had observed hypolobated megakaryorytes during chemotherapy for leukemia[12]. Similarly out of 82 cases observed megakaryocytic hyperplasia is 12.1% of cases.Fig [3].

Fra enil etal have observed increased mitotic index of the hematopoietic cells following intravenous dose of vincristine. Vincristine, a vinca alkaloid used in the treatment of lymphoma has antimitotic activity[13,14].

Gelatinous transformation of bone marrow has been reported following chemotherapy for myeloma[15].Pure red cell aplasia has been reported following chemotherapy for hodgkins lymphoma in 25 year old female. They found that MOPP/ABVD therapy induces immunoregulatory disturbance which results in emergence of autoreactive erythroid suppressors. The marrow finding showed normal myeloid and megakaryocyte lineage but there was marked suppression of erythroid precursors[16].

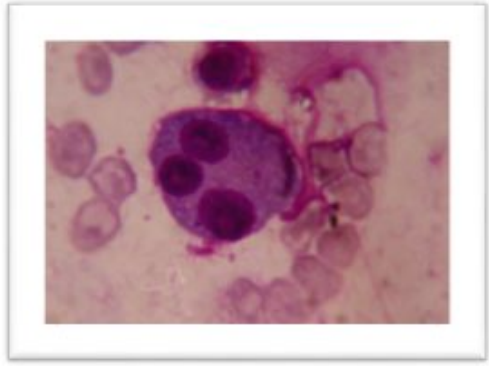
THERAPY RELATED MYELODYSPLASTIC SYNDROME:

t-MDS/t-AML are consequences of mutational effects caused by chemotherapy, radiotherapy or combination of both of these modalities .t-MDS, t-AML account for 10-20% of all cases of AML. The two factors namely cumulative dose and dose intensity of cytotoxic therapy determines the timing of development of t-MDS. t-MDS/t-AML typically occurs several months to years after chemotherapy. One study reveals that three phases occur,one is pancytopenia, myelodysplatic syndrome and finally leukemia[17].

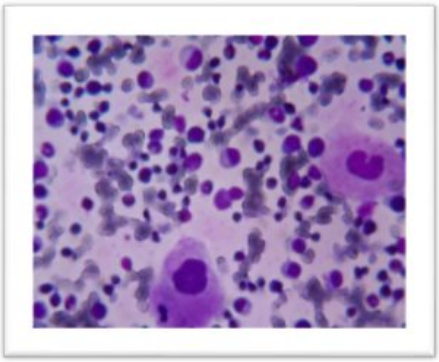
The dysplastic features commonly observed in MDS are megaloblastosis, multinuclearity, nuclear budding, intranuclear bridging, karyorrhexis and karyopyknosis and hypolobated megakaryocytes Of all the chemotherapeutic agents alkylating agents and topoisomerase II inhibitors are well known to cause therapy related leukemias .t-MDS, t- AML are consequences of mutational effects caused by chemotherapeutic agents. Not all the patients who receive chemotherapy develop second cancer, what predisposes these patients to develop therapy related MDS should be understood. Maintenance of genomic stability and DNA repair mechanism may be impaired in these individuals. In an attempt to prevent the complications of secondary AML/MDS improved initial treatment is to be given.

Some interesting findings we observed were occasional dyserythropoeitic and dysmyelopoetic cells. Fig[3].Few of our cases revealed hyperplasia of monolobated megakaryocytes. Fig[4] No metastatic deposits were observed is all 82 cases.

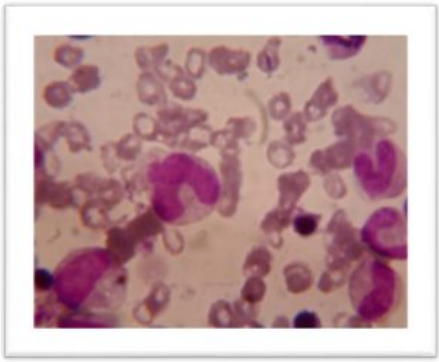
Fig[3].Photomicrograph of bone marrow smear showing trinucleated erythroblasts,(1000x).



Fig[4]:Photomicrograph of bone marrow smear showing many hypolobated megakaryocytes(1000x).



Fig[5]:Photomicrograph showing nuclear budding in cells of myeloid series.(1000x).



MDS with isolated del 5q syndrome is a distinct clinical category within the WHO classification of MDS. This is a disease of elderly women characterized by thrombocytosis with transfusion dependent anemia of macrocytic type which is therapy resistant. Marrow demonstrates large number of hypolobated forms of megakaryocytes with paucity of erythroid precursors. There is mild leucopenia and normal marrow blast count. The clinical course is mild and prognosis is good[17].

Dorothy [18] observed more megaloblastoid changes and dyspoietic changes in children who were treated with chemotherapeutic agents for ALL,AML and CNS tumours. There was marked suppression of erythroid series. The dyspoietic changes were more than those of primary MDS. Among the patients diagnosed with breast carcinoma in between 1992-1999 the overall leukemia incidence was 0.28%; AML/MDS was 0.11%.(Henry G Kaplan)[19].Risk of leukemia development following epirubicin therapy for breast cancer was more. Among the case which developed Leukemia AML L2 (2)cases,AML L3(1),AML M4(3),ALL(2) were recorded. Risk of leukemia increased when radiotherapy was combined with chemotherapy, standard incidence ratio was 28.5. Roberto Latagliata[20] has reported t- MDS in 5 patients out of 77 patients who received ATRA for acute prolymphocytic leukemia. When retrospective analysis of the cases which presented with leukemia was evaluated they found it was preceded by a phase of myelodysplastic syndrome followed by overt leukemia. The latent period for these changes to occur varied for many drugs, minimum of 1-2 years.

CONCLUSION:

Chemotherapeutic drugs are known to cause bone marrow suppression. Though bone marrow has enormous capacity to replenish the deficit, in certain patients severe myelosuppression occurs frequently causing anemia, febrile neutropenia, thrombocytopenia. Rarely they cause gelatinous transformation of marrow, bone marrow necrosis. These hemotogical toxicity following the chemotherapeutic drugs can force the clinician to reduce the dosage, prolonging the treatment duration. Cytopenia occurring during chemotherapeutic drug administration should be carefully evaluated; careful monitoring of the blood counts is essential ; long term follow up is also recommended as cytotoxic agents is known to cause second cancers, as studies have shown that cancer chemotherapeutic drugs are prone to cause therapy related myeloid neoplasms.

In our study the major hematological change observed was grade I-II anemia in 49%. Bone marrow aspiration study revealed Micronormoblastic maturation in 50%, both micro and macronormoblastic maturation in18.29% ,Megaloblastic change in 14.6% and 12.1% showed megakaryocyte hyperplasia with few dysmegakaryopoeitic cells.

Understanding the marrow proliferative capacity, age related marrow changes, general condition of patient; judicious use of chemotherapeutic agents with good knowledge of their mechanism of action would prevent 1% risk of second cancer occurring after treatment of primary cancer.

REFERENCES:

1. John D Boice,Lois B Travis.Body wars: Effect of friendly fire.J.Natl Cancer Inst,1995;87:10
2. Wickramasinghe SN ,Blood and Bone marrow pathology,Anna Porwit,ed 2,2011,ch1,p3.
3. Carter SK and MSlavik .Chemotherapy of Cancer,Annual Review of Pharmacology,1974,vol14:157-183.DOI:10.1146/annure.pa.14.040174.001105
4. Jerome E. Groopman,Loretta M.Itri .Chemotherapy –Induced Anemia in Adults :Incidence and Treatment ,J Natl Cancer Inst 1999;91:1616-34.
5. Bhavik D Doshi ,Nilesh M,Pandyal,Chirag A,Shah ,Ashish KGupta et al.Chemotherapy induced neutropenia in cancer patients with solid tumours in India ,Singhania university ,Pacherii Bari ,Jhunjhunu ,Raajastahn,Der Pharmacia Lettre,2012,4(2):584-590.
6. Bassam Abdul Rasool Hasan, Zuraidah Binti Mohd Yusuf,Mohammd Azmi Hassali,Saad Bin Othman.Association of neutropenia onset and severity with chemotherapy regimes and schedules,Pacific J CANCER Prev ,2011;12,1425-1428.
7. Mackall CL,TA Fleisher ,MR Brown ,IT Magrath,AT Shad,ME Horowiz etalLymphocyte depletion with intensive chemotherapy for cancer, Blood1 994;84: 2221-2228.
8. Victoria Rodrigeuz,Fernanado Cabanillas,Michael A.Burgess,Eugene M. Mckelvey, Manual Valdiviesco,Gerald P,Bodey ,Emil J.Freiech.Combination chemotherapy in advanced malignant lymphoma,1977:49(3).
9. Mitchell SCairo Dose reductions and delays:Limitations of myelosuppresive chemotherapy.Oncology sep 2000 14(sippl 8):21-31.
10. Aldestein DJ John D Hines .Bon emarrow morphological hanges after combination chemotherapy including VP-16,Cancer 56:467-471,1985
11. Monica Jain ,Seema Tyagi .Transient abnormal megakaryocytic hyperplasia secondary to all –Trans retinoic acid therapy ,ijpm,2012;55(2).
12. JeurgenThiele,Hans M,K Vansicka,Annete Schmitt-Graeff,Susanne Bandschuh etal.Effects of chemotherapy and interferon alfa on bone marrow morphological features in chronic myelogenous leukemia.AmJ Clin Pathol 2000;114:57-65.
13. Emil Frei II, Jacqueline Whang,Robert b.Scoggins etal.The Sathmokinetic effect of vincristine.Cancer Res1964;24:1918-25.
14. Rellick SL,O'Leary H,Piktel D,Walton C,Fortney JE et al.Bone marrow osteoblast damage by chemotherapeutic agents.PLos one7(2): e30758.doi: 10.1371/ journal.pone.0030758
15. Mary Mathew ,Issac Mathews ,Chetan manohar,Sripathi Rao.Gelatinous transformation of bone marrow following chemotherapy for myeloma, ijpm, 2001/:44(53-54).
16.. Bassam Abdul Rasool Hasan, Zuraidah Binti Mohd Yusuf,Mohammd Azmi Hassali,Saad Bin Othman.Treatment patterns and outcomes in management of solid cancer patient suffering from thrombocytopenia in Penang Hospital Asian Pacific J cancerPrev,2011;12,2841-2845.
17. SDMichelles,RW McKenna, DC Arthur ,RD Brunning .Therapy related acute myeloid leukemia and myelodysplastic syndrome:A clinical and morphological syudy for 65 cases.Blood ,1985,65:1364-1372.
18. Dorothy R.Barnard ,Beverly Lange,Todd A.Alonzo,Jonathan Buckley et al.Acute myeloid leukemia and myelodyspalstic syndrome in children treated for cancer;Comparison with primary presentation.Blood 2002 100:427-434.
19. Henry GKaplan,Judith A.Malmgen and Mary K Atwood.Increased incidence of myrlodysplatic syndrome and acute myeloid leukemia following breast cancer treatment with radiation alone or combined with chemotherapy /;A registry cohort analysis1990-2005BMC Cancer 2011 11;260.
20. Roberto Latagliata ,MC Pettit ,SFenu,Mancini ,Maria Antonietta Therapy related myelodysplastic syndrome –acute myelogenous leukemia in patients treated for acute promyelocytix leukemia.Blood 2002 99;822-824.