NEUTROPENIA FOLLOWING INDUCTION THERAPY IN ACUTE MYELOID LEUKAEMIA (AML) AND ROLE OF GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)

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Abstract:

Context: *This study was designed to observe the course of neutropenia that is onset of absolute neutropenia, depth of neutropenia and recovery pattern of neutropenia following induction chemotherapy and effect of granulocyte colony stimulating factor (G-CSF) on the course of neutropenia in adult acute myeloid leukaemia (AML) patients.*

Methods: *A total of 34 newly diagnosed, adult, de novo AML patients opted to receive induction chemotherapy were enrolled for this study. All of them were given induction chemotherapy with cytarabine and daunorubicin as per 2+5 protocol. Four of them were dropped from this study; 2 due to early death and 2 due to resistant disease so were treated with early alternative chemotherapy regimen. So the ultimate sample of this study was 30 patients. Out of them 13 were given G-CSF following chemotherapy. Absolute Neutrophil count (ANC) of all patients were followed up until full recovery.*

Results: *The difference in day of onset of absolute neutropenia (day 8 in G-CSF group vs. day 9 in no G-CSF group, P=.078) and number of day to reach nadir (day11 in G-CSF treated group vs. day12 in no G-CSF group, P=.688) was not significant between two group. The depth of neutropenia did not differ significantly as well (mean ANC 66/mm^3 vs. 102/mm^3, P=.184). However, recovery from absolute neutropenia was significantly (4 days) earlier in G-CSF treated patients (day 18 vs. day 22, P<.001). G-CSF treated patients also showed earlier attainment of ANC e"1,000/mm^3 (day 20 vs. day 25, P<.001) and ANC e"1,500/mm^3 (day 21 vs. day 27, P<.001). Duration of severe neutropenia was significantly shorter (9.6 days vs. 12.8 days P=.001) in G-CSF treated group.*

Key words: *Acute myeloid leukaemia (AML), neutropenia, Granulocyte colony stimulating factor (G-CSF)*

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Introduction:

The most common chemotherapy regimen for remission induction in acute myeloid leukaemia (AML) includes the use of cytarabine with an anthracycline, most commonly, daunorubicin. Cytarabine is administered for 7days with anthracycline on 1st 3 days. This combination is called 7 and 3 or 7+3 regimen. 7+3 regimen is superior to 5+2 and equivalent to 10+3, documented by all related studies.[1] Yet 5+2 regimen is widely used in Bangladesh due to poor socioeconomic status, lack of adequate supportive care facilities.

Remission induction as well as consolidation treatment of (AML) is associated with considerable morbidity and mortality. A significant component of the morbidity and mortality is related to the prolonged, severe neutropenia resulting from the disease as well as the intensive chemotherapy. The outcome of treatment is dependent, in part, on the ability of the patient to tolerate myelosuppression.[2] Neutropenia is an important factor predisposing to severe infection, resulting in significant morbidity and mortality rate despite standard therapy involving hospitalization and antibiotic treatment, in cancer patients.[3]

The risk of infection correlate closely with the degree as well as the duration of neutropenia.[4] Strategies to reduce the toxicities associated with intensive chemotherapy involved the uses of attenuated doses of standard regimen and myeloid growth factors. Although a decrease in early death rate can be achieved through dose

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reduction, response rates are less favourable due to inadequate antileukaemic cytotoxicities.[5] The use of granulocyte colony stimulating factor (G-CSF) as supportive therapy may allow the full dose of chemotherapy to be administered on time, so that the outcome of chemotherapy is not compromised.[6] There is no evidence that growth factors induce the growth of myeloid leukaemia cells, though the application of growth factors in AML has been limited by the theoretical concerns about their ability to stimulate the growth of myeloid leukaemia. [2, 7]

Materials and Methods:

The patients of this study were enrolled from the Department of Haematology, BSMMU and Department of Haematology, Dhaka Medical College Hospital. A total of 34 de novo AML patients, within the age of 15 to 60 years, newly diagnosed on the basis of peripheral blood and bone marrow examination, intended to receive induction chemotherapy was assigned for this study. Patients, morphologically diagnosed as AML-M_3 or acute promyelocytic leukaemia (APL), having absolute or severe neutropenia (ANC or absolute neutrophil count <500/cmm), having significantly impaired renal or hepatic function and having cardiac disorder like recent myocardial infarction, angina, arrhythmia, left ventricular failure etc, were excluded from this study. Out of these 34 patients 4 were dropped from this study; 2 because of early death, even before recovery from severe neutropenia and 2 due to resistant disease who underwent treatment with earlier alternative regimen.

All patients were given induction chemotherapy with cytarabine 100mg/m^2/day as 18 to 24 hour continuous intravenous infusion for 5 days and daunorubicin 45 to 60 mg/m^2/day as over 1 hour intravenous infusion for 1st two days. Out of 30 patients 13 were given G-CSF: 300 ìg of filgrastim subcutaneously daily starting 1to3 days after completion of chemotherapy intended to continue up to recovery from severe neutropenia or at least up to passing over expected nadir of neutropenia. G-CSF was discontinued following appearance of any blast in peripheral blood. ANC of all 30 patients was followed as per designed questionnaire until recovery from neutropenia.

Results and Observations:

The mean age of the G-CSF treated group and without G-CSF treated were 29 and 35.29 years respectively. The age difference between two groups was not significant (p=.166) (Table-I). In G-CSF treated group, out of 13 patients 7 were male and 6 ware female however in control group 12 were male and 5 were female. The mean body weight in kg of G-CSF treated group was 51.15±6.49 and that of without G-CSF treated group was 56.00±8.52, which did not differ significantly (p=.099). The number of doses of G-CSF given to the patients of G-CSF treated group was 4 to 9 with mean number of dose was 6. The G-CSF was started within day 7 to day 10 of the chemotherapy cycle; the median time of initiation of G-CSF was day 9.

The median time of onset of severe neutropenia was on day 8 and day 9 for G-CSF treated group and control group respectively (p=.078). The median time to reach nadir of neutropenia was on day 11 and day 12 for G-CSF treated group

Table-I

Age distribution of the patients

Age (years)	Number of Patients		p value*
	G-CSF (n=13)	No G-CSF(n =17)	
15 - 20	3 (23.1)	1 (5.9)	
21 - 30	7 (53.8)	7 (41.2)	
31 - 40	1 (7.7)	2 (11.8)	
41 - 50	1 (7.7)	5 (29.4)	
51 - 60	1 (7.7)	2 (11.8)	
Total	13 (100.0)	17 (100.0)	
Mean ± SD	29.00±11.409	35.29±12.424	0.166

Figures within parentheses denote corresponding percentage

*t test was done to measure the level of significance. P value d" 0.05 was considered as the level of significance.

and control group respectively (p=.688). The median time of recovery from severe neutropenia (ANC reached ≥500/mm^3) in G-CSF treated group and control group was on day 18 and day 22 (p<.001) respectively. G-CSF treated group recovered from moderate neutropenia (ANC reached ≥1000/mm^3) on the median time of day 20 versus day 25 in control group (p<.001). The median time of complete recovery from neutropenia (ANC reached ≥1500/mm^3) in G-CSF treated group was day 21 whereas control group recovered on day 27 (p<.001). The mean duration of severe neutropenia was 9.62 days in G-CSF treated group versus 12.82 days in control group (p=.001) (Table-II).

The mean baseline (the day before starting chemotherapy or day 0) ANC in G-CSF treated group and control group were 2754/mm^3 and 3950/mm^3 (p=.570) respectively. The mean ANC during nadir were 66/mm^3 and 102/mm^3 in G-CSF treated group and control group respectively (p=.184) (Table-III).

Table-II

Observations of the study groups after therapy

Event	Number of days		p value*
	G-CSF	No G-CSF	
Onset of severe neutropenia	8 (6-10)	9 (7-12)	0.078
ANC Reached Nadir on	11 (9-14)	12 (9-15)	0.688
ANC reached ≥500/mm^3	18 (15-21)	22 (19-27)	0.000
ANC reached ≥1000/mm^3	20 (17-23)	25 (22-31)	0.000
ANC reached ≥1500/mm^3	21 (19-24)	27 (23-35)	0.000
Duration of severe neutropenia	9.62±1.805	12.82±2.767	0.001

Figures within parentheses denote corresponding percentage

* t test was done to measure the level of significance. P value <0.05 was considered as the level of significance.

Table-III

Mean ANC before chemotherapy and during nadir.

Time	Mean ANC /mm^3		p value*
	G-CSF	No G-CSF	
Baseline	2754±2289#	3950±3226	0.570
During nadir	66±65	102±77	0.184

* t test was done to measure the level of significance. 0.05 was considered as a level of significance.

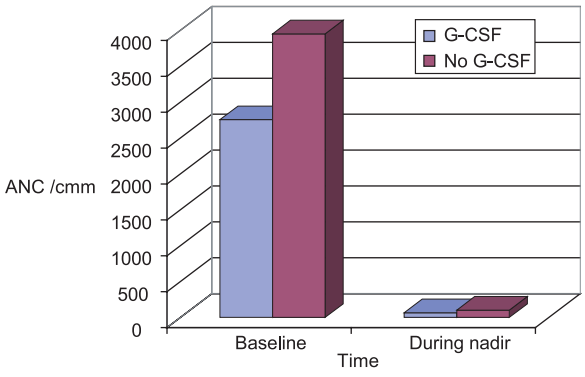

Fig.-1: *Mean ANC before chemotherapy and during nadir*

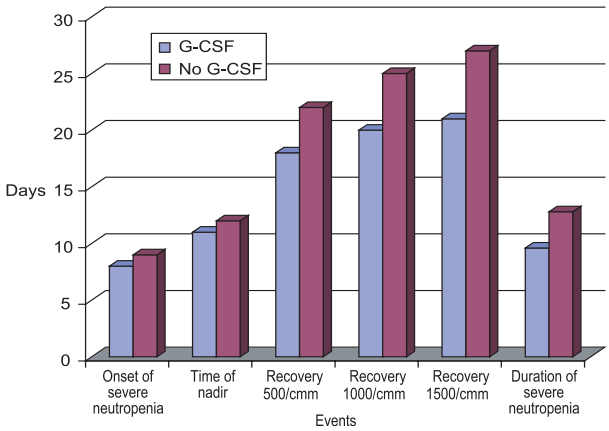

Fig.-2: *Onset, nadir and recovery pattern from neutropenia.*

Discussion:

Neutropenia is inevitable after induction chemotherapy with cytarabine and daunorubicin in AML.[8, 9] Both the duration and depth of neutropenia is closely related to the chance of infection.[4] So the goal of this study was to observe the course of neutropenia and the effect of G-CSF on the course of neutropenia.

In this study highest number of patient in both groups (7) was in the age range of 21 to 30 years. This observation contrasts with the worldwide age related incidence pattern of AML which shows the increasing incidence with increase of age.[1] This observation may be attributed to the lower number of patients are attending to the tertiary level of institution from higher age group, or more patients from younger age group opted for intensive chemotherapy, or very small non representative sample size. Possibility of different age related incidence pattern in Bangladesh can be searched for only by wide scale community based study. However the mean age of two groups (29.0 year in group A versus 35.3 year in group B, P=.166) were not significantly different. The mean ANC on the day before initiation of induction chemotherapy termed as baseline ANC did not differ significantly between two groups, which was 2,754/mm^3 in G-CSF treated patients and 3,950/mm^3 in without G-CSF treated patients (P=.266) (Figure-1).

G-CSF is supposed not to have any effect on the time of onset of severe neutropenia as the time of initiation of G-CSF was around the time of onset of severe neutropenia; the median time of onset of severe neutropenia in G-CSF treated patients were on day 8 which was very similar to the median time of initiation of G-CSF. The insignificant difference in time of onset of severe neutropenia, day 8 in G-CSF treated group versus day 9 in without G-CSF treated group (p=.078), probably indicate the selection biasness. The median time of ANC to reach nadir was day 11 (range 9-14) in G-CSF treated group and day 12 (range 9-15) in without G-CSF treated patients (p=.688), which did not significantly differ between two groups as well (Figure-2). According to literature nadir of cytopenia with the use of cytarabine results by 7 to 10 days after the therapy is ended, and daunorubicin causes cytopenia with nadir by 10 to 14 days.[8, 9]

In this study G-CSF has shown to significantly reduce the time of recovery from neutropenia after induction chemotherapy. The patients received G-CSF recovered from severe neutropenia, expressed as ANC e"500/mm^3, 4 days earlier than the patients not treated with G-CSF (median day 18 vs. day 22, P<.001). G-CSF treated patients reached at the ANC level of ≥1000/mm^3 5 days earlier than those who have not given G-CSF after induction (median day 20 vs. day 25, P<.001). Complete recovery from neutropenia expressed as ANC e"1500/mm^3 was attained 6 days earlier in G-CSF treated patients than others (median day 21 vs. day 27, P<.001) (Figure-2).

The recovery pattern of neutrophil count observed in this study was very similar to many studies conducted in this field. It has been shown in a randomized, double blind, placebo-controlled, phase III study of G-CSF in adult AML patient, conducted by the International Acute Myeloid Leukaemia Study Group, that G-CSF causes 5 days earlier recovery from absolute neutropenia (median day 20 vs. day 25, P=.0001) after induction chemotherapy with daunorubicin, cytarabine and etoposide as per 3+7+5 protocol.[1(2)] The same result was observed by a group of researchers in patients older than 60 years of age after induction chemotherapy with mitoxatrone, cytarabine and etoposide as per 3+7+3 protocol.[4,5] Another group of researchers for the Australian Leukaemia Study Group (ALSG) in New South Wales, Australia demonstrated that glycosylated recombinant human granulocyte colony-stimulating factor (lenograstim) causes 4 days earlier recovery from absolute neutropenia than the patient not treated with G-CSF (median day 18 vs. day 22, P=.0005) after induction chemotherapy with cytarabine, idarubicin and etoposide in AML patients.[10] It has been evidenced in another study that recovery from moderate neutropenia, that is ANC at the level of ≥1,000/mm^3 was achieved 6 days earlier in the AML patients treated with

growth factor after induction therapy (median day 21 vs. day 27, P<.001).[11]

The mean duration of severe or absolute neutropenia, measured as period from onset of absolute neutropenia to recovery from absolute neutropenia, was significantly reduced by the use of G- CSF. The values were 9.62 days for the patients treated with G-CSF and 12.82 days for the patients not supported by G-CSF (P=.001) (Figure- 2). The International Acute Myeloid Leukaemia Study Group have observed the similar (4 days) reduction in the duration of neutropenia with the use of G-CSF in comparison to patients not treated with G-CSF (median 10 days vs. 14 days, P=.015) after induction chemotherapy.[1(2)] A group of worker in the Department of Paediatrics, Beijing Medical University, also observed similar reduction in the duration of absolute neutropenia with the administration of G-CSF in children after intensive induction chemotherapy (median 5 days vs. 10 days, P<.05).[12]

The depth of neutropenia or lowest neutrophil count after chemotherapy, which was indicated by absolute neutrophil count during nadir, was not influenced by the use of G-CSF. The mean ANC during nadir of G-CSF treated patients were 66/mm^3 versus 102/mm^3 (P=.184) in patients not treated with G-CSF (Figure-1).

As the duration of neutropenia especially absolute neutropenia as well as the depth of neutropenia is closely related to the risk of infection, which should have direct impact on morbidity, mortality and economical burden, the observations in this study about onset, nadir and recovery of absolute neutropenia, may provide us some guidance about treatment planning like planning the time of isolation of post chemotherapy patients, planning necessary supportive measure according to risk assessment and assessing the rationality of use of G-CSF. Rationality of the use of G-CSF should be measured by considering the cost of G-CSF, against the cost for extra hospital stay and increased risk of infection and antibiotic requirement in less equipped centres like our.

American Society of Clinical Oncology (ASCO) recommends the use of G-CSF after postremission consolidation chemotherapy, as in most centres this chemotherapy is administered in the outpatient setting or during a brief hospital admission. G-CSF reduces the risk of infection by reducing the duration of severe neutropenia after this therapy. G-CSF use following induction chemotherapy is reasonable especially in patients older than 55 years of age.[13]

The main limitations of this study were small sample size, use of chemotherapy for shorter duration than recognized standard and lack of randomization. Patients treated with G-CSF were not selected randomly but according to clinical conditions of the patient; so the selection was biased. Another limitation of this study was that, most patients of the G-CSF treated group discontinued the administration of the G-CSF in an earlier time than the time was set in the protocol.

Conclusion:

Remission induction of AML patients with intensive chemotherapy is inevitably associated with severe neutropenia which is again most important predisposing factor to infection, resulting in concerning treatment related morbidity and mortality. These treatment related morbidity and mortality is attempted to minimize traditionally by taking several measures including strict isolation of neutropenic patients, barrier nursing, use of broad spectrum antibiotic, antifungal etc. Besides, the use G-CSF may be considered in an intend to reduce the duration of neutropenia, which in turn may reduce the duration of isolation and hospital stay, chance of infection and requirement of anti-infective agents. The use of G-CSF in post chemotherapy neutropenic patient should be considered in the light of its pharmacoeconomic impact.

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