Neutrophil recovery with or without G-CSF in non M3 AML patient with DA 3+7 protocol

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ABSTRACT

Background: Induction of acute myeloid leukaemia is associated with a high incidence of treatment related mortality mostly due to neutropenia related infections. This study primarily analyses the duration of neutrophil recovery with or without G-CSF during induction with DA 3+7 in non M3 AML patients. This study also evaluates role of G-CSF in duration febrile neutropenia, hospital stay, total blood products transfusion, total number of used injectable antibiotics and remission status. Methods: It was a Quasi Experimental - Non-Randomized Controlled Trail. There were two groups a) Case = Patients receiving G-CSF b) Control= Patients not receiving G-CSF. Sampling was purposive sampling. Results: 50 patients in two group, G-CSF group (n=25) and control group (No G-CSF) (n=25) participated in this study. Among them 54% was female and 46% was male. Median age of the participants was 28 years. Neutrophil recovery duration in G-CSF group vs control group showed 22.64 vs 24.64 days (p value 0.003). Duration of febrile neutropenia in G-CSF group vs control group showed 11.24 vs 13.56 days (p value 0.038). Duration of hospital stay in G-CSF group vs control group showed 23.64 vs 25.76 days (p value 0.002). Total number of blood and blood product transfusion in G-CSF group vs control group showed 3.80 vs 3.88 (p value 0.597). Total number of injectable antibiotics in G-CSF group vs control group showed 2.72 vs 3.12 days (p value 0.169). In G-CSF group 22 (88%) and in control group 23 (92%) were in complete remission (p value 0.637). Conclusions: G-CSF significantly reduces the duration of neutropenia (p value 0.003), febrile neutropenia (p value 0.038) and hospital stay (p value 0.002) after induction with DA 3+7. This may cause reduction in treatment cost and sepsis related mortality. G-CSF cannot significantly reduce use of blood products (p value 0.597) and injectable antibiotics (p value 0.169) after induction with DA 3+7. G-CSF does not affect morphological remission status (p value 0.637) after induction with DA 3+7.

Keywords: AML; Neutrophil Recovery; G-CSF; Induction therapy

Introduction

Acute myeloid leukaemia (AML) represents a heterogeneous group of haematologic malignancies arising from the transformation and expansion of an early myeloid stem cell. Induction chemotherapy comprising a combination of anthracycline and cytarabine especially DA 3+7 (Daunorubicin 60-90 mg/m2 daily for 3 days plus Cytarabine 100-200 mg/m2 daily for 7 days), is a standard treatment for
newly diagnosed patients with AML (Non M3 AML).\(^1\) Although this combination regimen provides fair anti-leukemic efficacy, it is associated with a high incidence of treatment related mortality mostly due to neutropenia related infection.\(^2\) The use of G-CSF in patients with acute myeloid leukaemia (AML) remained controversial because of the in vitro observation that leukemic cells express G-CSFR and that G-CSF could stimulate leukemic cell growth.\(^3,4\)

This study analyses the duration of neutrophil recovery with or without G-CSF during induction with DA 3+7 in non M3 AML patients. This study also analyses total number of transfusions, total number of antibiotics used, duration of febrile neutropenia, hospital stay and remission rate between G-CSF and non-G-CSF group.

**Materials and Methods**

All new and relapse cases of non-M3 AML patients undergoing induction with DA 3+7 in department of Haematology, DMCH were included in the study. Patients were divided into two subgroup- a. Receiving G-CSF during induction (Case) and b. Not receiving G-CSF during induction (Control). G-CSF was administered from D+11. G-CSF administration strategies were decided by the attending physicians, and the doses and routes of filgrastim administration were decided according to FDA guidelines.

Duration of neutropenia was defined as the median number of days from the start of induction chemotherapy to the time when an ANC>500/\(\mu\)L was achieved and maintained for 3 days in a row or 1000/\(\mu\)L or more in a single time. Chemotherapy induced febrile neutropenia (CIFN) was defined as development of fever after induction chemotherapy initiation with an ANC<500/\(\mu\)L.

Hospital stay was calculated as the median number of days from the start of induction chemotherapy to the date of discharge from the hospital.

All statistical analyses were done by IBM SPSS (Statistical Package for the Social Sciences) software package. At first distribution of data was determined by calculating Skewness and Kurtosis and data show asymmetric distribution. So, for hypothesis testing nonparametric tests were used. Remission status variable has qualitative data so, Chi-square test was performed. A p value of 0.05 was considered significant for this study. To see the correlation among variable Spearman’s correlation test was used.

**Results**

**Patient’s Characteristics**

The final participants were 25 in each group. Median age of study subjects was 28. Among the 50 participants (in two groups) 54% was female and 46% was male (Fig 1). 70% participants were in 20-50 age range group (Fig 2). Youngest was 14 years and oldest was 64 years.
Neutrophil recovery duration showed p value 0.003. So null hypothesis (H0) was rejected. G-CSF significantly reduces duration of neutropenia due to DA 3+7 chemotherapy in non M3 AML.

Duration of febrile neutropenia showed p value 0.038. So, null hypothesis was rejected. G-CSF significantly reduces duration of febrile neutropenia due to DA 3+7 chemotherapy in non M3 AML.

Duration of hospital stay showed p value 0.002. So, null hypothesis was rejected. G-CSF significantly reduces duration of hospital stay due to DA 3+7 chemotherapy in Non M3 AML.

**Total blood and blood products transfusion, Total number of injectable antibiotics**

Total number of blood and blood product transfusion showed p value 0.597 (Table I). So, H0 was accepted. G-CSF does not significantly reduce total number of transfusions during DA 3+7 chemotherapy in non M3 AML.

| Table I: All variables with sum, mean, SD, Maximum-Minimum and p Value |
|----------------|-----------------|-----------------|-----------------|-----------------|
|               | Sum | Mean with SD | Maximum-Minimum | P Value  |
| Neutropenia recovery duration | G-CSF | No G-CSF | G-CSF | No G-CSF | G-CSF | No G-CSF |
| Neutropenia recovery duration | 566 | 616 | 22.64 | 24.64 | 19-26 | 20-30 | 0.003 |
| SD±1.934 | SD±2.374 | a |
| Duration of Febrile Neutropenia | 281 | 339 | 11.24 | 13.56 | 6-15 | 6-25 | 0.038 |
| SD±2.619 | SD±4.436 | a |
| Hospital Stay | 591 | 644 | 23.64 | 25.76 | 20-28 | 21-32 | 0.002 |
| SD±2.139 | SD±2.587 | a |
| Total transfusion | 95 | 97 | 3.80 | 3.88 | 2-7 | 2-6 | 0.597 |
| SD±1.528 | SD±0.927 | a |
| Total Injectable Antibiotics | 68 | 78 | 2.72 | 3.12 | 1-5 | 1-6 | 0.169 |
| SD±0.936 | SD±1.054 | a |
| In Remission | 22 | 23 | 88% | 92% | 0.637 |

a = Mann-Whitney U test & Kruskal walli test  
b = Chi square test ,  G· CSF = Case; No G-CSF = Control  
SD = Standard Deviation
Discussion

G-CSF significantly reduces (p value 0.003) duration of neutropenia (22.64 vs 24.64 days) due to DA 3+7 chemotherapy in non M3 AML. Dombert et al conducted in 1995 in elderly patients (≥ 65 years) found neutrophil recovery 6 days earlier (21 days vs 27 days) with significant p value.5 Heil et al conducted in 521 young patients (≥ 16 years) in 1997 found that neutrophil recovery 5 days earlier (20 days vs 25 days) with significant p value and Ka-Won Kang et al conducted in 2016 with de novo AML patients with some result.6,7 There was total 315 participants. The participants were divided into three groups according to use of G-CSF- No use, preemptive (median of 9 days) and therapeutic (median of 11 days). This study shows neutrophil recovery among three groups were 27.5 days vs. 23 days vs. 24 days. It was statistically significant (p value <0.001). A vast number of other randomized trials of GCSF administration after induction chemotherapy in AML demonstrated a consistent reduction (by 2-6 days) in time to neutrophil recovery e.g. Godwin et al, 1998; Usuki et al, 2002, Lehrnbecher et al, Alonzo et al.8-11 However, Von Lilienfeld-Toal et al conducted in 2007 in elderly patients found neutrophil recovery 2 days earlier (17 days vs 19 days) with non-significant p value (0.67).12

G-CSF significantly reduces (p value=0.038) duration of febrile neutropenia (11.24 vs 13.56 days) due to DA 3+7 chemotherapy in non M3 AML. Ka-Won Kang et al a multicentre study with de novo AML patients showed significant reduction in duration of febrile neutropenia 6 days vs 10 days (p value <0.001).7 However, Alonzo et al, Godwin et al, 1998; Usuki et al, 2002, did not find significant decrease of duration of febrile neutropenia.8,9,11 G-CSF significantly reduces (p value 0.002) duration of hospital stay (23.64 vs 25.78) due to DA 3+7 chemotherapy in non M3 AML. This study showed strong correlation between neutrophil recovery and hospital stay. By reducing duration of neutropenia, we can reduce duration of hospital stay. Several studies like Amadori et al, Alonzo et al, Harrouseau et al found significant role of G-CSF in reducing hospital stay.11,13,14 However, Godwin et al, 1998 and Ka-Won Kang et al did not find any significant role of G-CSF in reducing hospital stay.7,8 G-CSF does not significantly reduce total number of transfusion (p value 0.597), total number of injectable antibiotics (p value 0.169) during DA 3+7 chemotherapy in non M3 AML. In G-CSF group 22 (88%) and in control group 23 (92%) was in complete remission. Chi-square test showed p value 0.637. So, G-CSF does not affect remission status after DA 3+7 induction in non M3 AML. There are some studies which use G-CSF to prime leukaemia cells to enhance their sensitivity to S-phase-specific agents but very few have shown successful results. One complex study (Estey et al, 1999) in poor-prognosis newly diagnosed AML found that the addition of G-CSF to chemotherapy improved the complete remission rate compared with chemotherapy alone.15 One may question rate of relapse and 5-year event free survival (EFS) in both groups. Lehrnbecher et al shows there is no significant deference in relapse rate at 5 year (p= 0.45) or 5y-EFS (p=0.66).10

References


2. D. Valcarcel, P. Montesinos, I. Sanchez-Ortega, et al. A scoring system to predict the risk of death during induction with anthracycline plus...


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