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# "To Evaluate the Adverse Effects of Erythropoietin According to CTCAE V4.03 Criteria in Patient Having Anemia with Chronic Kidney Disease"

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***Abstract:*** *CKD is recognized as a major health problem. Anemia is a well- known complication in chronic kidney disease, thus assessment of safety of erythropoietic drugs become necessary, since it is widely used in the treatment of anemia associated with CKD. CTCAE criteria grades condition of a patient on the basis of symptoms.The aim of present study is to evaluate the adverse effect of Erythropoietin according to CTCAE v4.03 criteria in patient having anemia in Chronic Kidney Disease. A prospective observational single centered study was conducted on 80 CKD patients in Nephrology department of NIMS Hospital, Jaipur from February. Observed Adverse events of subjects were graded according to CTCAE v4.03. In our study out of total parameters observed 37.38% was found to be Normal, 31.93% Mild, 15.68% Moderate, 12.38% Severe, 1.70% Life threatening. No Parameters was graded under Death. Safety of erythropoietin was considerable but the effectiveness was less than required. while considering the more expensive Blood transfusion, erythropoietin helps to cut-off high expenses and improve patient compliances.*

***Keywords:*** *Common Terminology Criteria for Adverse Events (CTCAE), Anemia, Erythropoietin, Chronic Kidney Disease.*

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## I. Introduction

Chronic kidney disease is defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (GFR), that persist for more than three months[1]. It is recognized as a major health problem affecting approximately 735 million people globally [2].

Out of all the indicators we consider GFR to be foremost for overall kidney function which equals the total amount of fluid filtered through all of the functioning nephrons per unit of time. In past few decades, the definition and classification of CKD had developed but ongoing definition for CKD according to international guideline is decreased kidney function shown by GFR of less than 60 mL/min per 1·73 m², or markers of kidney damage, or both, of at least 3 months duration. When GFR is less than 15 mL/min per 1·73m, a person has reached end stage kidney disease (ESKD), at this point kidney function is no longer able to support life for long period of time.

Anemia is a well- known complication in chronic kidney disease and associated with progression of CKD, poor quality of life, and increase in morbidity and mortality[3]. Greater hospitalization and mortality is also characterized by anemia in patients under hemodialysis[15].Severity of anemia worsen as GFR falls. Anemia might begin to develop in the early stages of CKD. Damaged kidneys are unable to produce the hormone erythropoietin which stimulate the bone marrow to create RBC. Red blood cells contain Hb, which delivers oxygen from lungs to the rest of your body.Fewer RBC mean less oxygen in your blood and that could result in anemia.

Anemia in CKD is mostly treated with erythropoietic drugs which stimulate or enhance the production of RBC. But the normal haemoglobin targeting using erythropoietic drugs shows harmful effects during its clinical trials so the level of Hb in anemic treating with erythropoietic drugs was limited to 10 to 11g/dl.

Use of erythropoietic drugs for the treatment helps cut-off the use of more expensive and complicated blood transfusion process thus improves patient compliances to the treatment. Still there is a lack of one-size-fit-all treatment protocol for erythropoietic drugs therefor highly individualization of treatment is required[14,15].

To assess patient safety and treatment related information we need precise capture and monitoring of symptomatic adverse events (AE) which is essential in clinical trials and drug labeling. In the United States, the standard approach for collecting this information as part of trials in oncology is clinician reporting using the Common Terminology Criteria for Adverse Events (CTCAE), which allows licensed clinicians to grade AEs

based upon descriptive clinical criteria. The duty of a given AE grade has inference for patient treatment and/or participation in clinical trials[27].

In CTCAE criteria we use grade system where we grade condition of a patient on the basis of symptoms. Generally, we use range 1 to 5 for grading where each range shows condition of a patient.

## II. Material and Methods

The study was carried out at the nephrology ward of NIMS tertiary care teaching hospital, Jaipur, Rajasthan, for a time frame of six months which got approved by Institutional ethical committee, NIMS University. A total of 80 subjects were enrolled in the study on the basis of inclusion and exclusion criteria. Data was collected which includes patient demographic details, vitals, Laboratory data. Subject was assessed using the laboratory data of a month. Adverse event found was classified according to CTCAE v4.03 criteria and the data were analysed using Microsoft Excel 2016.

## III. Results

- **Alkaline Phosphate**

**Table 1**Classification of Increased Alkaline Phosphate level according to CTCAE v4.03

| CTCAE Criteria | No. of patients | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 19 | 24% | 14(17.5%) | 5(6.25%) |
| **Mild (1)** | 56 | 70.00% | 31(38.75%) | 25(31.25%) |
| **Moderate (2)** | 4 | 5% | 3(3.75%) | 1(1.25%) |
| **Severe (3)** | 1 | 1.25% | 1(1.25%) | 0 |
| **Life threatening (4)** | 0 | 0 | 0 | 0 |
| **Death (5)** | 0 | 0 | 0 | 0 |

**Result:** Out of 80 patients 19 (24%) of patients shows normal Range of Alkaline Phosphate and the rest 61 (76.25%) patients shows an increased ALP level which were classified according to CTCAE v4.03 Criteria as Mild 56 patients (70%), Moderate 4 patients (5%), Severe 1 patient (1.25%). There was no patients ALP level raised up to Life Threatening level or death. In all classification of Alkaline Phosphate Male has a higher than females.

- **Alanine Aminotransferase**

**Table 2**Classification of Increased Alanine Aminotransferase level according to CTCAE v4.03

| CTCAE Criteria | No. of patients | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 15 | 18.75% | 7(8.75%) | 8(10%) |
| **Mild (1)** | 47 | 58.75% | 28(35%) | 19(23.75%) |
| **Moderate (2)** | 4 | 5% | 3(3.75%) | 1(1.25%) |
| **Severe (3)** | 14 | 17.50% | 11(13.75%) | 3(3.75%) |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** In the observed values of ALT out of 80 patients 15 patients (18.75%) shows normal values in which 7(8.75%) males and 8(10%) females are present. In the rest are classified accordingly as per CTCAE v4.03 Criteria as Mild 47 patients (58.75%) in which 28(35%) males and 19(23.75%) females , Moderate 4 patients (5%) where 3(3.75%) males and 1 (1.25%) females, Severe 14 Patients (17.50%) where 11(13.75%) males and 3(3.75%) females are present. And there were no one falls under Life threatening level of Death.

- **Anxiety**

**Table 3**Classification of Increased Anxiety according to CTCAE v4.03

| CTCAE Criteria | No. of patients | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 20 | 25.00% | 13(16.25%) | 7(8.75%) |
| **Mild (1)** | 26 | 32.50% | 15(18.75%) | 11(13.75%) |
| **Moderate (2)** | 27 | 34% | 15(18.75%) | 12(15%) |
| **Severe (3)** | 7 | 8.75% | 5(6.25%) | 2(2.5%) |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Anxiety was observed in the patients about their disease condition and out of 80 patients 20 patients (25%) was normal and the rest was classified on the basis of CTCAE v4.03 criteria as 26 Patients (32.50%0 was observed to be suffering from Mild Anxiety, 27 patients (34%) from Moderate, 7 patients (8.75%) from severe Anxiety. Life threatening Symptoms of Anxiety was not observed. Anxiety was more observed in males in each classes over females.

- **Aspartate Aminotransferase**

**Table 4**Classification of Increased Aspartate Aminotransferase level according to CTCAE v4.03

| CTCAE Criteria | No. of patients | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 39 | 48.75% | 23(28.75%) | 16(20%) |
| **Mild (1)** | 37 | 46.75% | 22(27.5%) | 15(18.75%) |
| **Moderate (2)** | 3 | 3.75% | 3(3.75%) | 0 |
| **Severe (3)** | 1 | 1.25% | 1(1.25%) | 0 |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Increased Aspartate Aminotransferase (AST) was observed in patients which was classified according to CTCAE v4.03 and find out that out of 80 patients 39 (48.75%) was found to be normal and rest comes under Mild 37 Patients (46.75%), Moderate 3 Patients (3.75%), Severe 1 patient (1.25%).There was no Patients fall under the category of Life threatening condition or Death. In each class males show an increased no. over females.

- **Blood Pressure**

**Table 5**Classification of Increased Blood Pressure according to CTCAE v4.03

| CTCAE Criteria | No. of patients | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 6 | 7.50% | 4(5%) | 2(2.5%) |
| **Mild (1)** | 12 | 15% | 6(7.5%) | 6(7.5%) |
| **Moderate (2)** | 17 | 21.25% | 11(13.75%) | 6(7.5%) |
| **Severe (3)** | 45 | 56.25% | 28(35%) | 17(21.25%) |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Out of 80 Patients 6 (7.50%) was found to have lower BP than Hypertensive range. The rest Hypertensive Patients was classified according to CTCAE v4.03 as Mild 12 patients (15%), Moderate 17 patients (21.25%), Severe 45 patients (56.25%), and no patients falls under Life threatening and Death category. In each class males show an increased no. over females expect for Mild category where both are equal.

- **Edema**

**Table 6**Classification of Edema condition according to CTCAE v4.03

| CTCAE Criteria | No. of population | Percentage | Male | Female |
|---|---|---|---|---|
| **Normal (0)** | 50 | 62.50% | 32(40%) | 18(22.5%) |
| **Mild (1)** | 13 | 16% | 7(8.75%) | 6(7.5%) |
| **Moderate (2)** | 12 | 15% | 6(7.5%) | 6(7.5%) |
| **Severe (3)** | 5 | 6.25% | 2(2.5%) | 1(1.25%) |
| **Life threatening (4)** | 0 | 0 | 0 | 0 |
| **Death (5)** | 0 | 0 | 0 | 0 |

**Result:** Out of 80 patients 50 of them were found to be normal without edema, 13 patients (16%) falls under Mild condition, 12 Patients (15%) falls under Moderate, 5 Patients (6.25%) under Severe condition according to CTCAE v4.03 criteria. There were no patients falls under Life threatening classification or Death. In each class males show an increased no. over females except in moderate category where they both are equal.

- **Haemoglobin**

**Table 7**Classification of Increased Haemoglobin level according to CTCAE v4.03

| CTCAE Criteria | No. of patients | Percentage | Male | Female |
|---|---|---|---|---|
| **Normal (0)** | 2 | 2.50% | 1(1.25%) | 1(1.25%) |
| **Mild (1)** | 21 | 35.00% | 17(21.25%) | 4(5%) |
| **Moderate (2)** | 27 | 33.75% | 19(23.75%) | 8(10%) |
| **Severe (3)** | 28 | 35.00% | 10(12.5%) | 18(22.5%) |
| **Life threatening (4)** | 2 | 2.50% | 2(2.5%) | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Out of 80 patients level of Hb was normal for 2 patients (2.50%) where 1 (1.25%) each male and female. Abnormal level of Hb was classified according to CTCAE v4.03 criteria as Mild 21 patients (35%) where 17(21.25%) male and 4(5%) female, Moderate 27 patients (33.75%) where 19(23.75%) males and 8(10%) females, Severe 28 patients (35%) where 10(12.5%) males and 18(22.5%) females, Life threatening 2

patients (2.50%) where both are males. There was no Death occurred.

- **Potassium**

**Table 8**Classification of Increased Serum Potassium level according to CTCAE v4.03

| CTCAE Criteria | No. of population | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 21 | 26.25% | 8(10%) | 13(16.25%) |
| **Mild (1)** | 16 | 20% | 12(15%) | 4(5%) |
| **Moderate (2)** | 22 | 27.50% | 14(17.5%) | 8(10%) |
| **Severe (3)** | 8 | 10% | 4(5%) | 4(5%) |
| **Life threatening (4)** | 13 | 16.25% | 9(11.25%) | 4(5%) |
| **Death (5)** | 0 | 0% | 0 | 0 |

**Result:** Out of 80 patients Serum Potassium level was normal for 21 patients (26.25%) in which 8(10%) males and 13(16.25%) females. And the increased serum potassium level was classified according to CTCAE Criteria as 16 patients in Mild category (20%) where 12(15%) males and 4(5%) females, 22 patients in Moderate (27.50%) where 14(17.5%) males and 8(10%) females, 8 patients in Severe (10%) where 4(5%) each male and female, 13 patients falls under Life threatening (16.25%) where 9(11.25%) males and 4(5%) females, and no one falls under Death.

- **Shortness of Breath**

**Table 9** Classification of Shortness of Breath according to CTCAE v4.03

| CTCAE Criteria | No. of population | Percentage | Male | Female |
|---|---|---|---|---|
| **Normal (0)** | 27 | 33.75% | 16(20%) | 11(13.75%) |
| **Mild (1)** | 26 | 32.50% | 19(23.75%) | 7(8.75%) |
| **Moderate (2)** | 16 | 20% | 9(11.25%) | 7(8.75%) |
| **Severe (3)** | 11 | 13.75% | 5(6.25%) | 6(7.5%) |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Out of 80 patients Shortness of Breath was not observed in 27 patients (33.75%) where 16(20%) males and 11(13.75%) females. And it is classified according to CTCAE v4.03 in patients with SOB as 26 patients in Mild category (32.50%) where 19(23.5%) males and 7(8.75%) females, 16 patients in Moderate (20%)where 9(11.25%) males and 7(8.5%) females, 11 patients in Severe (13.75%) where 5(6.25%) males and 6 (7.5%) females, No patients fall under Life threatening and Death.

- **Vomiting**

**Table10** Classification of Vomiting according to CTCAE v4.03

| CTCAE CRITERIA | No. of population | Percentage | Male | Female |
|---|---|---|---|---|
| **Normal (0)** | 63 | 78.75% | 40(50%) | 23(28%) |
| **Mild (1)** | 11 | 13.75% | 6(7.5%) | 5(6.25%) |
| **Moderate (2)** | 6 | 7.50% | 3(3.75%) | 3(3.75%) |
| **Severe (3)** | 0 | 0.00% | 0 | 0 |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Out of 80 patients Vomiting was not observed in 63 patients (78.75%). And it is classified according to CTCAE v4.03 in patients had vomiting as 11 patients in Mild category (13.75%), 6 patients in Moderate (7.50%), No patients fall under Sever, Life threatening and Death. In each class males show an increased no. over females expect in moderate where they are equal.

- **Pain**

**Table 11**Classification of Pain according to CTCAE v4.03

| CTCAE Criteria | No. of population | Percentage | Males | Females |
|---|---|---|---|---|
| **Normal (0)** | 57 | 71.25% | 36(45%) | 21(26.25%) |
| **Mild (1)** | 16 | 20% | 9(11.25%) | 7(8.75%) |
| **Moderate (2)** | 5 | 6.25% | 2(2.5%) | 3(3.75%) |
| **Severe (3)** | 2 | 2.50% | 2(2.5%) | 0 |
| **Life threatening (4)** | 0 | 0.00% | 0 | 0 |
| **Death (5)** | 0 | 0.00% | 0 | 0 |

**Result:** Out of 80 patients 57 (71.25%) was not suffering from pain and the rest are classified as Mild 16 patients (20%), Moderate 5 patients (6.25%), Severe 2 patients (2.50%). Life threatening and Death was found to be 0 according to CTCAE v4.03 Criteria

## IV. Discussion

In our study the sample size was 80 as per the calculation in which subjects are recruited according to the inclusion and exclusion criteria in which 31(38.75%) females and 49 (61.25%) Male subjects were participated. Eleven parameters which was mentioned in the product leaflet was accepted for the grading using CTCAE v4.03 Criteria, even though CTCAE Criteria has developed for the classification of Adverse events related to cancer treatment, its feasibility is been checked with other conditions also so as to monitor treatment related Adverse events improvise the treatment.

CKD is recognized as a major health problem affecting approximately 735 million people globally[2]. Anemia is a well- known complication in chronic kidney disease and associated with progression of CKD, poor quality of life, and increase in morbidity and mortality[3]. Use of erythropoietic drugs for the treatment helps cut-off the use of more expensive and complicated blood transfusion process thus improves patient compliances to the treatment[14]. Thus, assessment of safety of erythropoietic drugs become necessary, since it is widely used in the treatment of anemia associated with CKD in both dialysis and non-dialysis patients.In our study out of total parameters observed 37.38% was found to be Normal, 31.93% Mild, 15.68% Moderate, 12.38% Severe, 1.70% Life threatening and no Parameters was graded under Death.

Erythropoietin is used to treat anemia associated with CKD, which helps improve the Hb level. Although there are some controversial issues in the maintenance of normal haemoglobin level due to the increased cardiovascular risk, so the recommended target of haemoglobin by clinical practice guidelines are 10 to 11 g/dl[14,15]. which comes under Mild grading according to CTCAE v4.03. The observed data shows that Only 2.50% of population falls under Normal. Abnormal level of Hb was classified according to CTCAE v4.03 criteria as 35% Mild, 33.75% Moderate, 35% Severe, and only 2.50% Life threatening. There were no parameters graded under Death. After all there is a small percentage of Life-threatening grade and higher percentage falls under Severe and Moderate grade which requires medical intervention, efficacy of erythropoietin is less than required still while considering the more expensive Blood transfusion, erythropoietin helps to cut-off high expenses and improve patient compliances[14].

## V. Conclusion

According to this study, the safety of erythropoietin was considerable.As majority of observed data falls under Normal and Mild grading except for a bit of severe and Life-threatening events. The efficacy of erythropoietin was not satisfying, as per the observed data there is a small percentage of Life-threatening grade and higher percentage falls under Severe and Moderate grade. Still it cuts off the expenses of Blood transfusion method which helps to improve patient compliances.

CTCAE v4.03 which was developed for monitoring drug related adverse events in the treatment of cancer was fit to evaluate the abnormal values observed adverse effect of erythropoietin in the treatment of anemia associated with CKD. There was no grade to fit the observed normal values in the CTCAE v4.03 was the only drawback observed while using it in the study. Grade provided for normal values helps to compare the prevalence of abnormalities in reference to the normal outcomes.

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