INTRODUCTION

Anemia is one of the major problems in patients receiving cancer chemotherapy for which blood transfusions or erythropoietin stimulating agents (ESAs) are considered. ESAs have demonstrated promising roles in decreasing transfusion requirement, improving hemoglobin levels and quality of life (QOL). Out of 11 RCTs including 6,849 participants, 9 RCTs reported 2,312 deaths with overall mortality of 33.7%. Mortality reported for epoetin alfa (EA), epoetin beta (EB) and darbepoetin alfa (DA) was 41.24%, 73.1% and 8.99% respectively. TEEs reported for EA, EB and DA were 5.88%, 9.28% and 2.85%, respectively. Serious adverse events were 39.04%, 36.29%, 1.53% for EA, EB and DA, respectively. Tumor progression for EA and EB was 37.53% and 95.46%, respectively. No tumor progression was reported with DA. Erythropoietin reported no mortality, TEEs, serious ADRs and tumor progression. About 9% patients required transfusions during ESA therapy. Current evidence suggests that use of ESA reduces transfusion need but increases mortality and risks of TEEs.

ABSTRACT

The impact of erythropoiesis stimulating agents (ESAs) on clinical outcomes among breast cancer patients is debatable. Current review is aimed to ascertain the efficacy of ESAs among breast cancer patients. Randomised controlled trials (RCTs) were electronically searched. Primary outcomes were mortality, blood transfusion requirements and thromboembolic events (TEEs); whereas, secondary outcomes were safety, tumor progression, anemia treatment, hemoglobin levels and quality of life (QOL). Out of 11 RCTs including 6,849 participants, 9 RCTs reported 2,312 deaths with overall mortality of 33.7%. Mortality reported for epoetin alfa (EA), epoetin beta (EB) and darbepoetin alfa (DA) was 41.24%, 73.1% and 8.99% respectively. TEEs reported for EA, EB and DA were 5.88%, 9.28% and 2.85%, respectively. Serious adverse events were 39.04%, 36.29%, 1.53% for EA, EB and DA, respectively. Tumor progression for EA and EB was 37.53% and 95.46%, respectively. No tumor progression was reported with DA. Erythropoietin reported no mortality, TEEs, serious ADRs and tumor progression. About 9% patients required transfusions during ESA therapy. Current evidence suggests that use of ESA reduces transfusion need but increases mortality and risks of TEEs.

Key Words: Chemotherapy, Randomised controlled trials, Anemia, Breast cancer, Erythropoiesis stimulating agents, Mortality, Tumor progression, Survival, Quality of life, Transfusion requirements, Safety.

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SYSTEMATIC REVIEW

Effect of Erythropoiesis Stimulating Agents on Clinical Outcomes in Breast Cancer Patients: A Systematic Review of Randomised Controlled Trials

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review was based on full-text assessment. Dissent among researchers concerning the worth of studies was resolved through discussion and mutual consent. All RCTs conveying the effect of ESAs in BC were included. Studies conducted on other types of cancers, published in language other than English and having ambiguous inclusion were excluded. Primary outcome measures were mortality, blood transfusion requirements and thromboembolic events (TEEs). Secondary outcome measures were safety, tumor progression, anemia treatment, hemoglobin levels and quality of life (QOL).

Employing a pre-structured data collection form (DCF), data were independently extracted by two authors (MK & FN). All the studies were evaluated to determine the effect of ESAs on predefined clinical outcomes (Figure 1).

RESULTS

Characteristics of selected studies:

Eleven RCTs reporting the predetermined outcomes with the use of ESAs were included in current review. The risk of bias within studies was assessed on the PRISMA criteria (Figure 2). All RCTs were adequately randomised, and appropriately concealed; most trials gave follow-up status up to last extent. Blinding of patients was done in only three trials.9,11,17 One trial stopped early for benefits and all the studies followed the intent to treat principle.11

RCTs were conducted on 6,849 BC patients with CIA of age ≥18 years (Table I). Four trials were conducted in Germany,14-17 four were located in multiple countries11-13,18 and the remaining three were from Italy, USA and Canada each,9-10

The interventions were ESAs in varying doses and frequencies with chemotherapy. Five RCTs had once weekly dosing,9-12,18 two had twice weekly dosing14,15 and four RCTs had thrice weekly dosing.8,13,16,17

All trials had at least one predefined outcome measure. Timings of outcome measures varied with different follow-up duration in these trials.

Impact of ESAs on clinical outcomes:

Nine trials reported mortality ranging from 1.9% to 73.1% in interventional group (IG) and 6% to 72.8% in control group (CG), suggesting the higher mortality in IG. However, only one study (Aapro et al.12) reported
| Authors | N | IG | CG | Age | Duration | SC stage | Dose | Frequency | Dose | Frequency | Co-intervention | F |
|---------|---|----|----|-----|----------|----------|------|-----------|------|-----------|---------------|---|
| Bel Mastri et al., 1997 | 62 | 31 | 31 | 29-68 | I | 28 months | EA - 150U/kg + MC same as CG | 3 times weekly | E - 60mg/m² | C - 600mg/m², E- 600mg/m² | Every 2 weeks | Ferrous sulfate 325 mg/d in specific cases | 6 months |
| O'Shaughnessy et al., 2006 | 100 | 51 | 49 | >18 | I-III | 10 months | EA - 40,000 U, increased to 60,000 U if Hb level did not improve | Once weekly | Placebo + MC | Once weekly | - | Monthly |
| Chang et al., 2005 | 354 | 177 | 177 | >18 | I-IV | 7 months | EA - 40,000 U + MC same as CG | Once weekly | SC + MC | Once weekly | 200 mg/day oral iron | Weekly |
| Jones et al., 2005 | 939 | 469 | 470 | >18 | I-IV | 12 months | EA - 40,000 U + MC same as CG | Once weekly | Placebo for 12 months | Once weekly | - | 3 months |
| Apurba et al., 2010 | 223 | 110 | 113 | >18 | I-IV | 19 months | EA- initiated at 10,000 IU/5000 IU if patient weight <65kg | 3 times weekly | BSC + MC | - | Iron supplementation | Monthly for 6 months then 3 months annually |
| Untch et al., 2011a | 733 | 356 | 377 | 18-65 | I-IV | 32 months | DA- 4.5 µg/kg/body weight + Chemotherapy Same as CG | E- 90 mg/m² + C- 600 mg/m² by T-175 mg/m² (ECT), OR E-150 mg/m² followed by T-225 mg/m² with PF (5 µg/kg/d, d3-d10) followed by CMF (C-500 mg/m² M-40 mg/m², F-600 mg/m²) on days 1 and 8 (ET₆T₈₃-CMF) | same as CG | q4d x 3 | - | Annually |
| Untch et al., 2011b | 733 | 356 | 377 | 18-65 | I-IV | 32 months | DA- 4.5 µg/kg body weight + Chemotherapy Same as CG | Q2W | E-90 mg/m² + C-600 mg/m² followed by T-175 mg/m² (ECT), OR E-150 mg/m² followed by T-225 mg/m² with PF (5 µg/kg/d, d3-d10) followed by CMF (C-500 mg/m² M-40 mg/m², F-600 mg/m²) on days 1 and 8 (ET₆T₈₃-CMF) | q2d x 4 | q2d x 3 | - | Annually |
| Mabouza et al., 2013 | 643 | 324 | 319 | 18-65 | I-III | 53 months | EA- 150 IU/kg + Chemotherapy Same as CG | 5 times weekly- Started on Day 1 upto Day 14 after 1DD chemotherapy- Sequential administration of each of three cycles of E-(150 mg/m² intravenously as a bolus infusion), T-(225 mg/m² intravenously as a 3-hour infusion), and C-(250 mg/m² intravenously as a 2-hour infusion), respectively, All patients received filgrastim SC (5 µg/kg body weight per day) from days 3 to 10 of each cycle. | 200 mg/day oral iron | - | 200 mg/day oral iron | Annually |
| Rizzi et al., 2014 | 1,234 | 615 | 619 | >18 | I-IV | 53 months | EA- 300µg-600µg + MC same as CG | 3 times weekly | SC + MC | - | Oral & IV iron therapy | Annually |
| Jones et al., 2016 | 2,098 | 1,050 | 1,048 | >18 | I-IV | 100 months | EA-40,000IU + MC same as CG | Once Weekly | BSC + MC | - | - | Annually |

**Table I: Summary of included studies evaluating effects of ESA on various outcomes in breast cancer patients.**

**Notes:**

- IDD= Intense Dose Dense, E=Epirubicin, T=Paclitaxel, C= Cyclophosphamide, M=Methotrexate, F= Fluorouracil, PF= Pegfilgrastim, EA=Epoetin Alfa, EB=Epoetin Beta, A/T BC= Anthracycline and/or Taxane Based Chemotherapy, DA= Darbepoetin Alfa, IG= Intervention Group, CG= Control Group, BSC= Best Standard Care, SC= Standard Care, MC= Myelotoxic Chemotherapy, FLC= First-Line Chemotherapy, G-CSF = Granulocyte Colony-Stimulating Factor.
statistically insignificant difference in mortality rate between both groups. Highest mortality rate was observed with EB.\textsuperscript{12}

Eight trials reported transfusion requirements for anemia ranging from 0% to 14.2% in IG and 0% to 28.1% in CG. Moebus et al.\textsuperscript{16} reported considerably higher transfusion rate in CG (28.1%) than IG (12.8%). Need of transfusions was statistically higher in IG as compared to CG in six trials (Table II). Studies using DA reported lowest transfusion rate.\textsuperscript{15}

TEEs were reported in eight trials ranging from 2.8% to 16% in IG and 0.8% to 14% in CG, suggesting the higher events in IG. A statistically higher proportion of TEEs in IG were reported in five trials (Table II).

Nine studies reported adverse events (AEs) ranging from 0.28% to 57.6% in IG and 0.28% to 60% in CG. Serious AEs included extra-cardiac, erythrocyte, platelet, bleeding/clotting, gastric/duodenal, small/large bowel and mucous membrane disorders. Two studies indicated statistically higher AEs in IG as compared to CG. (Table III).\textsuperscript{11,17} DA is associated with minimum number of ADEs in patients.\textsuperscript{15}

Five trials reported tumor progression ranging from 41% to 95.2% in IG and 43% to 96% in CG, indicating the

### Table II: RCTs evaluating effects of ESAs on mortality, transfusion requirements and thromboembolic events.

| Author, Year | Mortality | Transfusion Requirements | Thromboembolic Events |
|--------------|-----------|-------------------------|-----------------------|
| Del Mastro et al., 1997\textsuperscript{8} | Total | IG | CG | p-value | Total No. of patients receiving transfusion | IG | CG | p-value | Total No. of thromboembolic events | IG | CG | p-value |
| O’Shaughnessy et al., 2005\textsuperscript{9} | 1 | 1.9% | | | | | | | | |
| Chang et al., 2005\textsuperscript{10} | 51 | 13.5% | 15.2% | | 55 | 8.6% | 22.9% | <0.0001 | 33 | 10.8% | 7.8% | | |
| Jones et al., 2005\textsuperscript{11} | 249 | 28% | 23% | 0.02 | 113 | 10% | 14% | 0.06 | 141 | 16% | 14% | | |
| Aapro et al., 2008\textsuperscript{12} | 338 | 73.1% | 72.8% | 0.522 | 96 | 14.2% | 27% | 70.001 | 43 | 12.5% | 6% | 0.012 | |
| Pronzato et al., 2010\textsuperscript{13} | 43 | 20.9% | 17.7% | 0.86 | 26 | 7.5% | 16.5% | 0.059 | 5 | 3.6% | 0.8% | | |
| Untch et al., 2011\textsuperscript{14} | 107 | 17% | 13% | 0.450 | | | | | | | | | |
| Untch et al., 2011\textsuperscript{15} | 1 | 0.28% | 0% | - | 32 | 6% | 3% | 0.055 | | | | | |
| Moebus et al., 2013\textsuperscript{16} | 116 | 19% | 17% | | 131 | 12.6% | 28.1% | <0.0001 | 33 | 7% | 3% | 0.030 | |
| Nitz et al., 2014\textsuperscript{17} | 70 | 5.4% | 6% | 0.77 | | | | | 24 | 3% | 1% | 0.013 | |
| Jones et al., 2016\textsuperscript{18} | 1,337 | 64.8% | 63% | | 180 | 5.6% | 11.4% | <0.001 | 44 | 2.6% | 1.4% | 0.038 | |

| Author, Year | Safety | Tumor progression | Hemoglobin levels |
|--------------|--------|-----------------|-----------------|
| Del Mastro et al., 1997\textsuperscript{8} | No decline | Decline | <0.001 |
| O’Shaughnessy et al., 2005\textsuperscript{9} | 93 | 92.1% | 6.1% | 0.001 |
| Chang et al., 2005\textsuperscript{10} | Incidence similar between both groups | 100 | 51.4% | 5.1% | 0.001 |
| Jones et al., 2005\textsuperscript{11} | 357 | 42% | 34% | 0.02 | 394 | 41% | 43% | 0.98 | 59% | 45% | 0.001 |
| Aapro et al., 2008\textsuperscript{12} | 168 | 42% | 31% | | 442 | 95.2% | 96% | 0.448 | 68% | 14% | 0.001 |
| Pronzato et al., 2010\textsuperscript{13} | 34 | 16.5% | 14.4% | | | No differences found | 62% | 28% | 0.001 |
| Untch et al., 2011\textsuperscript{14} | 2 | 0.28% | 0.28% | | No deleterious effects | No significant change | Significant Decline | | |
| Moebus et al., 2013\textsuperscript{16} | 73 | 10% | 13% | | | No deleterious effects | No significant change | Significant Decline | <0.001 |
| Nitz et al., 2014\textsuperscript{17} | 28 | 3.3% | 1.3% | 0.013 | | No deleterious effects | No significant change | Significant Decline | <0.001 |
| Jones et al., 2016\textsuperscript{18} | 1,237 | 57.6% | 60% | | 1,241 | 58.1% | 60.1% | | | |

IG=Intervention Group, CG=Control Group.

### Table III: RCTs evaluating effects of ESAs on safety, tumor progression and hemoglobin levels.

| Author, Year | Safety | Tumor progression | Hemoglobin levels |
|--------------|--------|-----------------|-----------------|
| Del Mastro et al., 1997\textsuperscript{8} | No decline | Decline | <0.001 |
| O’Shaughnessy et al., 2005\textsuperscript{9} | 93 | 92.1% | 6.1% | 0.001 |
| Chang et al., 2005\textsuperscript{10} | Incidence similar between both groups | 100 | 51.4% | 5.1% | 0.001 |
| Jones et al., 2005\textsuperscript{11} | 357 | 42% | 34% | 0.02 | 394 | 41% | 43% | 0.98 | 59% | 45% | 0.001 |
| Aapro et al., 2008\textsuperscript{12} | 168 | 42% | 31% | | 442 | 95.2% | 96% | 0.448 | 68% | 14% | 0.001 |
| Pronzato et al., 2010\textsuperscript{13} | 34 | 16.5% | 14.4% | | | No differences found | 62% | 28% | 0.001 |
| Untch et al., 2011\textsuperscript{14} | 2 | 0.28% | 0.28% | | No deleterious effects | No significant change | Significant Decline | | |
| Moebus et al., 2013\textsuperscript{16} | 73 | 10% | 13% | | | No deleterious effects | No significant change | Significant Decline | <0.001 |
| Nitz et al., 2014\textsuperscript{17} | 28 | 3.3% | 1.3% | 0.013 | | No deleterious effects | No significant change | Significant Decline | <0.001 |
| Jones et al., 2016\textsuperscript{18} | 1,237 | 57.6% | 60% | | 1,241 | 58.1% | 60.1% | | | |
higher tumor progression in CG (Table III). EB is associated with maximum tumor progression rates\textsuperscript{12} as compared to EA.\textsuperscript{11}

Nine trials reported hemoglobin (Hb) change during ESA treatment. Of these, five trials reported that maintaining Hb was significant in IG ranging from 51.4% to 92.1%.\textsuperscript{8,13} Hb was maintained 5.1% to 45% patients in CG. Three trials reported significant Hb decline in CG.\textsuperscript{8,15,16} (Table IV). Maximum Hb maintenance is reported with EA.\textsuperscript{9}

Five out of 11 trials reported data on anemia treatment. Two trials used FACT-An Scale for scoring where Pronzato \textit{et al.},\textsuperscript{13} reported 14.2% change of score in IG and -0.5% in CG. Nitz \textit{et al.},\textsuperscript{17} reported no significant difference of scores between IG and CG. Other three trials described percentage of patients with anemia free survival ranging from 82.6% to 97.2% in IG and 72% to 93.9% in CG (Table IV). Maximum rate of anemia treatment was associated EA.\textsuperscript{10,18}

QOL was assessed in 7 RCTs. Of these, three trials demonstrated no impact on QOL with the use of ESAs.\textsuperscript{11,12,17} O’Shaughnessy \textit{et al.} \textsuperscript{9} reported improvements in QOL in 78.4% in IG and 71.4% in CG using LASA scoring. Pronzato \textit{et al.},\textsuperscript{13} reported results by CLAS Scale. Moebus \textit{et al.},\textsuperscript{16} was unable to report QOL due to missing baseline data. All three scales provided statistically significant improvement in QOL in IG (Table IV). EA therapy showed maximum improvements in QOL score.\textsuperscript{10}

**DISCUSSION**

Anemia frequently occurs among cancer patients receiving chemotherapy.\textsuperscript{16} ESAs provide survival benefits from CIA in patients with BC.\textsuperscript{17} Anthracycline therapy as FEC combination including 5-fluorouracil with epirubicin, and cyclophosphamide induces anemia in almost 42% patients.\textsuperscript{16} Current review has analysed the impact of several ESAs on various outcomes among patients with BC.

The high mortality rate after using ESAs is attributed to repopulating capability of tumor from a single stem cell in BC. Reinbothe \textit{et al.} suggested that erythropoietin receptor (EpoR) protein is expressed in breast tumor cells, where it seems to stimulate proliferation by erythropoietin-independent mechanism in estrogen receptor positive (ER\textsubscript{α}+), expressing in metastatic breast cancerous cells.\textsuperscript{23} Phillips \textit{et al.} revealed that over expression of an erythropoietin receptor (EpoR) amplified the clonogenicity of cancer cells resulting in increased mortality after using ESAs.\textsuperscript{24} Abundant expression of c-Myc in many cancers is another reason of tumor progression with the use of ESAs.\textsuperscript{25} EPO also increases MYC expression in erythroid progenitor cells. MYC is a family of regulator genes as well as proto oncogenes that code for transcription factors.\textsuperscript{26}

Previous studies revealed that treatment with epoetin alfa sustained and/or enhanced Hb concentration and patient reported outcomes (PROs).\textsuperscript{10} Several quantitative analysis provides evidence of Hb elevation with the use of ESAs, thereby reducing the need of RBCs transfusion.\textsuperscript{1,10} Further clarification might include elevated oxygenation of tissue having tumor at greater Hb points.\textsuperscript{27} Cancer cells become unaffected by tumor hypoxic conditions, raised oxygenation inhibits hypoxia preserving tumor cells to be sensitive to radiation, and cytostatic therapy. Hypoxia is more prevalent in anemic patients.\textsuperscript{27} Epoetin was initially used as optional treatment therapy for adjustment of anemia to avoid transfusions.\textsuperscript{28} European guidelines suggest the dose of erythropoietin as once weekly for patients having Hb between 9 to 11 g/dL with target Hb of 12-13 g/dL.\textsuperscript{12}

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**Table IV: RCTs evaluating effects of ESAs on anemia treatment and quality of life.**

| Outcomes | Anemia treatment | Quality of life** |
|----------|------------------|-----------------|
| Author, Year | Total No. of patients treated | IG p-value | CG p-value | Total No. of patients with increased QOL | IG | CG | p-value |
| Del Mastro \textit{et al.}, 1997\textsuperscript{8} | - | - | - | - | - | - | - |
| O’Shaughnessy \textit{et al.}, 2005\textsuperscript{9} | - | - | - | - | - | - | - |
| Chang \textit{et al.}, 2005\textsuperscript{10} | 333 | 97.2% | 90.9% | - | 166 | 93.8% | -95.4% | <0.0001 |
| Jones \textit{et al.}, 2005\textsuperscript{11} | - | - | - | - | - | - | - |
| Aspro \textit{et al.}, 2008\textsuperscript{12} | 359 | 82.6% | 72% | <0.01 | 166 | 93.8% | -95.4% | <0.0001 |
| Pronzato \textit{et al.}, 2010\textsuperscript{13} | - | 14.2% change from baseline | -0.5% change from baseline | 0.002 | 18.6% change from baseline | -2.7% change from baseline | 0.003 |
| Untch \textit{et al.}, 2011\textsuperscript{14} | - | - | - | - | - | - | - |
| Untch \textit{et al.}, 2011\textsuperscript{15} | - | - | - | - | - | - | - |
| Moebus \textit{et al.}, 2013\textsuperscript{16} | Not presented due to missing baseline data | - | - | - | - | - | - |
| Nitz \textit{et al.}, 2014\textsuperscript{17} | Not presented due to missing baseline data | - | - | - | - | - | - |
| Jones \textit{et al.}, 2016\textsuperscript{18} | 1,992 | 96% | 93.9% | - | 1,666 | 93.8% | -95.4% | <0.0001 |

IG=Intervention Group, CG=Control Group; *Assessed by FACT-An Scale; **Assessed by FACT-An, CLAS Scale and LASA Scores.
Antithrombotic therapy should be reserved for patients with Hb <10 g/dL to achieve targeted Hb 12 g/dL. Pronzato et al. estimated better tolerability of epoetin alfa with few AEs including thromboembolic events. Though occurrence of venous thrombosis was similar in both groups but serious thrombovascular events were more prevalent in IG receiving epoetin alfa. The drugs for BC have been connected with higher risk of venous TEEs due to thrombus formation in venous circulation. TEs may reside due to both superficial venous thrombosis and deep venous thrombosis. TEEs can be determined primarily by the differences in underlying cancer population due to disease stage and activation of the coagulation system after using ESAs. Coagulation pathways in BC are precised in Figure 2. ESAs can activate tumor cells to produce TF and cancer procoagulant (CP), which can start the extrinsic pathway by activating certain coagulation factors (VIIa and Xa). Thrombin causes platelet accumulation which intensifies the thrombophilic state. Hereafter, TF can initiate a hypercoagulability state with thrombosis.

Since thrombotic events are second leading cause of death in cancer patients, thromboprophylaxis improves prognosis and QOL in BC patients by inhibiting the thrombotic events. However, several regulatory authorities have limited the use of ESAs for CIA. Existing data underscored the association of epoetin and darbepeptin with TTEs and amplified mortality. Similar findings have been reported in composite analysis of previous studies. However, epoetin alfa therapy caused substantial decrease in transfusion requirements as well as improvement in QOL.

Del Mastro et al. reported that EPO prevents anemia and maintained Hb values along with prevention of anemia among receiving chemotherapy consisting of six cycles (cyclophosphamide, epirubicin, and fluorouracil (CEF) on day 1, every two weeks using granulocyte colony stimulating factor, subcutaneously from day 4 -11). The improved erythropoiesis with EPO therapy led to quick reduction of iron supply as evidenced by decline in iron/transferrin levels in plasma and overall iron stores assessed by total iron binding capacity. The boosted EPO-induced erythropoiesis is predictable to produce low level of ferritin. Representation of RBC is performed by estimation of mean corpuscular Hb (MCH), mean corpuscular volume (MCV), and mean corpuscular Hb concentration (MCHC). Clinically, anemia does not occur in EPO group due to maintenance of Hb levels.

CONCLUSION

Current review suggests that ESAs are generally well endured and can shield against anemia. With the exception of risks of thrombotic complications, ESAs appear to be harmless for the treatment or fundamental anticipation of anemia in CIA. Current evidence also ascertains that ESAs reduce the need for blood transfusions. However, risks of increased mortality and TEEs should not be disregarded during the treatment.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS’ CONTRIBUTION:
YHK: Conceptualised the plan for the current study; assisted in interpreting the results; assessed the data quality and approved the final version of the manuscript for submission.
SS, THM, MK: Did the literature search, screening and data extraction.
RN, NJ: Performed critical appraisal of all included studies.
THM: Drafted the manuscript; assessed the data quality and approved the final version of the manuscript for submission.

All authors have critically reviewed the manuscript.

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