

Selected Summary

Erythropoietin for Prevention or Treatment of anemia in Cancer Patients Undergoing Radiotherapy; Time to Pause and think !

Henk M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized, double blind placebo-controlled trial.

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SUMMARY

A multicentric randomized double-blind placebo controlled trial was carried out from March 1997 onwards to evaluate the benefit of erythropoietin administration to head and neck cancer patients in terms of cancer control and survival.

Patients with histologically proven squamous cell cancer of the head and neck region were included. Two categories of patients were included: patients receiving adjuvant post-operative radiation and patients receiving radical radiotherapy. Patients receiving adjuvant radiation were stratified according to the type of resection (R0 / R1 / R2). Hemoglobin levels of <12 g/dl for women and <13 g/dl for men were required for inclusion in the study.

Erythropoietin beta (epoietin β) was administered at dose of 300 IU/kg subcutaneously three times per week and placebo group patients received injection of a placebo solution. In addition, intravenous / oral iron therapy was added to patients with low iron stores (low transferrin saturation). When patients reached the target hemoglobin level of 14 g/dl for women and 15 g/dl for men or the hemoglobin level increased by more than 2 g/dl within 1 week, treatment was discontinued, to be resumed if hemoglobin concentration fell below the target concentration.

Radiation was administered to a dose of 60 Gy (range 56-64 Gy) for adjuvant RT in R0 / R1 resection status and 70 Gy (range 66-74 Gy) for R2 resection or for radical radiotherapy. RT was administered using 6 MV linear accelerator.

Primary endpoint of the study was loco regional progression-free survival.

Twenty three centers in Austria, France, Germany, and Switzerland participated in the study; and, 351 patients (171 in the placebo and 180 in the epoietin arm) were enrolled from March 1997 to April 2001. There were a high number of radiotherapy violations in both groups (54 in the placebo arm and 60 in the epoietin arm).

The mean radiation dose was 63.1 Gy in the placebo arm and 62 Gy in the epoietin arm. Overall, 82% of the study arm patients achieved target values of hemoglobin compared to only 15% in the placebo arm.

In the intention to treat analysis, 208 patients (59%) and loco regional tumour progression or died during follow-up: 92 in the placebo arm and 116 in the study arm. The relative risk for loco regional progression free survival was 1.62 for epoietin arm (95% CI 1.22-2.14, $P=0.0008$) and median PFS was 745 days in the placebo arm and 406 days in the epoietin arm. Analysis of the group of patients that received correct RT as per protocol, the relative risk for loco regional PFS was 1.42 (CI 1.01-2.01, $p=0.04$) and median PFS was 795 days and 551 days for placebo and study arms. In another analysis restricted to patients that received all treatment as per protocol, relative risk for loco regional PFS was 1.35 (CI 0.94-1.95, $p=0.11$) and median PFS was 749 days and 605 days for placebo and study arms ($p=0.8$).

A subgroup analysis was carried out in relation to the stratification groups (stratum 1: R0 resection patients, stratum 2: R1/R2

resection status, stratum 3: radical RT). Stratum I patients had comparable results in both arms, stratum 2 patients had a very poor outcome in the epoietin arm, and stratum 3 patients had a slightly worse outcome in the epoietin arm.

Multivariate analysis was also carried out and it supported the fact that epoietin beta administration was associated with a poor outcome. In univariate analysis, hemoglobin concentrations at start of treatment and time adjusted hemoglobin concentrations (area under curve) correlated with loco regional PFS.

Based on these results, the authors conclude that administration of erythropoietin beta leads to improvement in hemoglobin levels in patients receiving radiotherapy but is not associated with an improved outcome. In fact there is a possibility that the survival may be impaired in the group receiving erythropoietin. The impairment in survival in the study arm as compared to the placebo arm is not explained by any identifiable difference in the known prognostic factors among the two groups but can not be totally ruled out.

The authors have raised the possibility of biological effects of erythropoietin in non-erythroid cells, particularly the malignant cells as a mechanism impinging on outcome and survival in addition to the influence on hemoglobin levels. Thus, they suggest that further trials on erythropoietin should focus the question of cancer control survival in addition to quality of life issues. In addition, more research is required in understanding the biology of hemoglobin effect on survival and other effects of erythropoietin.

DISCUSSION

The results of this paper do come as a big surprise. It is common knowledge by now that tumour hypoxia is an important factor in poorer response to radiotherapy.¹ Since oxygen carrying capacity of the blood is linked to hemoglobin levels, low hemoglobin levels are an important factor contributing to tumour hypoxia.² Many studies have tried to correlate survival of patients in relation to hemoglobin levels and found that low hemoglobin levels are associated with poor long term survival.^{3,5} It would thus be

natural to expect that increasing the hemoglobin levels should improve the outcome in cancer patients undergoing radiation. Conventionally, blood transfusions have been the means to achieve this. There are two theoretical reservations with this the immunosuppressive effect of blood transfusion that has been shown to be detrimental in colorectal cancer and suspected to be detrimental in other malignancies and the fear of transfusion associated infections such as hepatitis, HIV, etc. With the availability of recombinant human erythropoietin, it was found that a powerful tool is available to increase hemoglobin levels and thus avoid blood transfusions in many situations. Erythropoietin administration has proved to be a boon to patients with chronic renal disease who have a high incidence of anemia and their problem is chronic.

Malignancy is another setting where many factors co-exist to cause anemia and treatment with chemotherapy and radiation also contributes to the problem. It has been shown that quality of life improves significantly in patients treated with erythropoietin to maintain or increase hemoglobin levels during chemotherapy or radiotherapy.⁶ Recent studies have tried to focus on the issue of survival. Some recent studies suggested that erythropoietin usage can lead to an improved survival in patients who had low hemoglobin levels.^{7,8}

How do we explain the results of this study. One of the possibilities is that there is an unbalanced distribution of some other prognostic factors in the two treatment arms. Though such an imbalance is not apparent, it can not be entirely ruled out. Secondly, some questions can be raised about the high protocol violation rate in the study. There were 54 radiotherapy violations in the placebo arm and 60 radiotherapy violations in the study arm. In addition, the mean dose of radiation to placebo arm patients was 63.1 Gy compared to 62 Gy for the study arm. Though the difference is small, it would be worthwhile to ponder if this is responsible for some of the difference in the outcome. The reason for considering this is that small incremental dosage can have a large effect

on radiation outcome both in terms of disease control and side effects.

High rates of protocol violations have reduced the statistical power of the study. This is apparent from the very large 95% confidence intervals of the results. This dilutes the significance of the study findings to some extent.

In spite of all these reservations, we should not neglect the results of the study. Firstly, let us consider if there is any possible reason for impairment of outcome in the study arm. An important observation is the difference in deaths due to non-cancer related events. Five patients in the placebo arm died of cardiac disorders compared to 10 in the study arm. In addition, one patient in the placebo arm died of general disorders (as mentioned in the paper,[?] details) compared to nine patients in the study arm. Thus, it is possible that erythropoietin beta led to a higher incidence of disease-unrelated but treatment-related deaths. Have such fatal side effects been noted in other studies too? A recent publication by Wun et al⁹ in Cancer has reported increased incidence of symptomatic venous thrombosis in patients with cancer of uterine cervix treated with chemo-radiotherapy and erythropoietin. Seventeen of 75 patients receiving erythropoietin had symptomatic venous thrombosis compared to two of 72 patients that did not receive erythropoietin. The odds ratio for developing venous thrombosis was 10.3 in the erythropoietin group.

Are there any other possibilities? It is imperative that we think about the interaction of erythropoietin with non-erythroid cells in the human body including tumour cells. It has been shown that various body cells have erythropoietin receptors. What is the role played by these receptors in the normal physiology is not clear at present. However, a recent publication in Seminars in Oncology presented a rationale for use of erythropoietin as a neurocognitive radioprotectant.¹⁰ They studied two mouse models where administration of erythropoietin prevented cognitive impairment caused by whole brain RT.

Overall, it can be said that we should not jump headlong to the conclusion being projected in many recent publications that administration of recombinant erythropoietin in anemic patients improves survival. More work is required in this field to answer the following questions.

1. What is the exact relation between hemoglobin levels and tumour control probabilities during radiotherapy? Whether the worse outcome noted with low hemoglobin levels or an improvement in outcome with treatment change linearly with hemoglobin level or there are threshold levels in upward or downward directions?
2. It is important to realize that erythropoietin takes time to improve hemoglobin levels. If hemoglobin levels at start of treatment are low, should patients receive blood transfusions to raise hemoglobin? What should be the target hemoglobin level at start of treatment? Glaser et al⁷ in 2001 showed that hemoglobin levels below 14.5 were associated with a worse outcome. In India, and probably in many other countries, usual hemoglobin levels at start of treatment are from 9 gm/dl to 10 gm/dl and blood transfusions are administered below this level. Should we be targeting higher hemoglobin levels (>14.5 gm/dl for males and >12.5 gm/dl for females) in all patients undergoing curative radiotherapy? What would be the impact of multiple blood transfusions in this setting, as erythropoietin is still beyond the financial capacity of majority of Indian patients.
3. Are there any major differences in the biological properties of erythropoietin alpha and beta? The study under discussion was carried out with erythropoietin beta while a larger volume of work on erythropoietin has been carried out using epoietin alpha.
4. The effect of erythropoietin on different body tissues including tumour tissues and

tumour tissue vasculature need to be studied in detail and clearly defined.

5. Tumour hypoxia is related to two factors: the oxygen carrying capacity of the blood and presence of poorly perfused areas in the tumour. Increasing hemoglobin levels will not be able to take care of the second problem. Thus, hypoxic cell sensitization should also continue to be explored and we should be trying to evaluate a combination of erythropoietin therapy and hypoxic cell sensitizers especially for large bulky tumours that have a high likelihood of poorly perfused areas.

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