Review Article

The safety of erythropoietin stimulating agents in surgical patients with head and neck squamous cell carcinoma—a narrative review

Megan-Lee Rogers[1]^, Milap Rughani[2]

[1]Ophthalmology Department, Sunshine Coast University Hospital, Birtinya, QLD, Australia; [2]Plastics and Reconstructive Surgery Department, Royal Brisbane and Women's Hospital, Brisbane, Australia

Contributions: (I) Conception and design: ML Rogers; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: ML Rogers; (V) Data analysis and interpretation: ML Rogers; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Megan-Lee Rogers. Attn Megan Rogers C/O Ophthalmology Department Caloundra, Caloundra Hospital, West Tce Caloundra 4551, Birtinya, QLD, Australia. Email: rogers.megan@outlook.com.

Objective: To determine whether the use of erythropoietin stimulating agents (ESAs) in patients with head and neck squamous cell carcinoma (HNSCC) undergoing surgical management is contraindicated.

Background: ESAs are commonly used adjuncts for anaemia management in select patient populations. HNSCC patients can be vulnerable to multifactorial anaemia, and it is commonly identified as a modifiable risk factor preoperatively. Anaemia contributes to tumour hypoxia which influences the degree of treatment resistance. Strong evidence linking anaemia with poorer locoregional control and overall survival in HNSCC has led researchers to pursue therapies which may improve haemoglobin levels. Despite correcting haemoglobin levels, the use of ESAs in HNSCC patients has failed to demonstrate an improvement in disease free survival or overall survival. Research in HNSCC patients undergoing primary radiotherapy demonstrates clear trends towards increased rates of locoregional failure and mortality, though research in surgical patients is lacking.

Methods: A narrative review was conducted of research in the English language with no date range limitation. A search was conducted of PubMed and CINAHL databases using the following MeSH terms: "erythropoietin", "squamous cell carcinoma", "squamous cell carcinoma of head and neck", "HNSCC", "epoetin" and "surgery".

Results: Studies in patients with HNSCC receiving ESA therapy during primary curative intent surgical management was limited. A total of 457 studies were identified, from this there were no studies reporting outcomes in patients treated with primary surgical management alone. From studies of HNSCC patients receiving radiotherapy as primary or adjuvant therapy, the use of ESAs was associated with increased risk of locoregional recurrence and mortality.

Conclusions: Despite a lack of research investigating surgical cohorts with HNSCC, the clear trend towards early locoregional failure and mortality amongst patients with advanced HNSCC receiving primary curative-intent radiotherapy on ESA therapy is suggestive of their relative contraindication. Several good quality randomised controlled trials have detected significant differences in rates of locoregional recurrence and overall survival. These studies and the issuing of a black box warning by the FDA should alert clinicians to this risk. Future research aimed at stratifying the risk for surgical patients may be of benefit in early disease when the risks are less well documented.

Keywords: Squamous cell carcinoma of head and neck; carcinoma, squamous cell; erythropoietin; anemia; head and neck neoplasms

Received: 20 June 2021; Accepted: 25 February 2022; Published: 13 October 2022.

doi: 10.21037/ajo-21-21

View this article at: https://dx.doi.org/10.21037/ajo-21-21

^ ORCID: 0000-0002-4519-7623.

Introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy in Australia accounting for 980,000 new cases per year (1). Head and neck squamous cell carcinoma (HNSCC) represents a significant disease burden for the Australian population, with 4,157 new cases diagnosed in 2019 (an incidence of approximately 14 cases per 100,000 population) (2). There are existing guidelines for how practitioners should manage HNSCC as an entity however the individual circumstances of the patient, including their medications, should also inform treatment options. In the routine work up for surgery patients undergo preoperative screening for modifiable risk factors, such as smoking status and anaemia, to reduce the risk of the perioperative period and improve clinical outcomes.

There is a large body of existing evidence regarding poor outcomes associated with the use of erythropoietin stimulating agents (ESAs) in cancer patients. There is however a paucity of literature regarding considerations for patient undergoing surgery and the use of ESAs. We aim to explore the literature regarding ESAs and its impact upon surgical outcomes in HNSCC. We will provide of the pharmacological background of ESAs, its cellular mechanisms and its use in the HNSCC patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://www.theajo.com/article/view/10.21037/ajo-21-21/rc).

Background

Anaemia is well recognised as a poor prognostic factor for those with HNSCC. (3) The aetiology of anaemia for HNSCC patients is often multifactorial and can include mechanical factors such as dysphagia and odynophagia, environmental factors such as smoking, alcohol consumption and metabolic factors, and treatment related effects such as xerostomia and mucositis. Systemic anticancer and inflammatory responses with the release of cytokines (importantly tumour necrotic factor alpha, interleukin-1, interferon gamma) have also been linked (4). Irrespective of the cause, anaemia contributes to the degree of tumour hypoxia associated with HNSCC. This directly influences the intrinsic resistance of the tumour to chemotherapy and radiotherapy though less is known about the surgical implications of hypoxia. Hypoxia is a well-known factor in radio-resistance and efforts to eliminate the hypoxic tumour environment have been well studied since the 1950s (5). Mechanisms to improve hypoxia such as oxygen delivery, correcting anaemia with transfusion and ESAs, administration of hypoxic radiation sensitisers such as nitroimidazoles and the newer hypoxic cytotoxins, preferentially targeting hypoxic cells and targeting of the vascular supply of hypoxic tumours have been trialled (6). Improving hypoxia has been demonstrated to improve treatment outcomes, locoregional control and survival for patients receiving chemotherapy and radiotherapy (RT) (7). Some studies address the impact of preoperative anaemia on HNSCC surgical patient outcomes, with one study of glottic cancers demonstrating a significantly worse five-year locoregional control for patients with pre-operative anaemia (8). Trials investigating whether ESAs would be a useful adjunct to improve haemoglobin levels and correct hypoxia have been performed in the broader cancer population as well as those with HNSCC receiving primary curative intent radiotherapy. Good quality research has revealed both poorer locoregional recurrence and overall survival in HNSCC patients receiving ESAs with concurrent RT; in one study, the use of ESAs was a higher independent prognostic factor for poor outcomes than smoking (9,10). Research investigating outcomes for those undergoing surgical interventions is lacking, though data from patients treated with primary radiotherapy showing an increase in mortality suggests their relative contraindication.

Historic and current use of ESAs

Erythropoietin (EPO) is a hormone that is synthesised in the kidneys and liver in response to tissue hypoxia. EPO primarily acts via the EPO-receptor (EPOR) pathway to increase the viability and production of red blood cells by stimulating erythroid progenitor cells in bone marrow. First isolated from human tissues in 1977, EPO was subsequently approved in 1989 as a treatment for anaemia in chronic kidney disease and remains a cornerstone in therapy when used in conjunction with iron therapy (11-13). The use of ESAs including epoetin alfa, epoetin beta and darbepoetin alfa, has been shown to decrease the need for blood transfusion (8,14,15). Potential benefits include symptomatic relief from anaemia as well as improved quality of life (16). Indications for use of ESAs includes for patients with anaemia due to chronic kidney disease, select patients undergoing chemotherapy, during treatment for HIV and in the perioperative period for select populations undergoing major surgery (17).

During early use, patients were titrated to target

haemoglobin (Hb) levels of 11–12 g/dL (15). Subsequent research and surveillance data revealed that targeting higher haemoglobin levels (≥13 g/dL) led to an increase in adverse outcomes including hypertension, stroke, vascular access thrombosis as well as trends towards increased myocardial infarction and mortality (12). A large body of evidence has also demonstrated that ESA use increased mortality rates for all cancer patients, with one large meta-analysis of 13,933 cancer patients demonstrating a trend towards increased mortality rate during the active study period of 17% and worsened overall survival of 6% (15). Clinical prescribing patterns responded by creating individualised haemoglobin targets based on symptoms and tolerating lower haemoglobin levels. Current expert opinion from the American Society of Clinical Oncology and American Society of Haematology 2019 guidelines suggest avoiding ESA use for cancer patients undergoing curative intent therapy (18).

Cellular mechanisms of hypoxia and treatment resistance

Anaemia contributes to tumour hypoxia which influences the degree of treatment resistance. In solid malignancies like HNSCC, tumours demonstrate variable degrees of hypoxia throughout as a result of rapid proliferation and angiogenesis. Response to chemotherapy is dependent upon drug delivery to abnormal tumour cells. Knowledge of the mechanism of ionizing radiation is important in understanding the resistance of hypoxic tumour cells. Radiation induces ionization of target cell DNA, producing free radicals which cause strand breaks in the DNA. The presence of oxygen makes this damage permanent by reacting with the free radicals. Under hypoxic conditions where oxygen is a limited substrate, compounds containing sulfhydryl (SH) groups can repair this damage to the DNA (19). Radiation sensitivity thus relies upon the presence of oxygen to induce permanent DNA damage and cell apoptosis, and as such hypoxic regions are less radiosensitive. Hypoxia thus contributes to disease invasiveness and metastatic potential, induces further angiogenesis and thus becomes increasingly resistant to treatment.

Recent studies have shown overexpression of EPO and EPOR in HNSCC may play a role in disease progression and invasiveness. EPO has downstream effects on both normal and tumour cells, and has been implicated in stimulating growth, affecting apoptosis and in drug resistance (20). Under hypoxic conditions, EPO binds and activates EPOR via the hypoxia-inducible factor (HIF) pathway, producing hypoxia-inducible proteins and their downstream products such as HIF-1a, HIF-2a and carbonic-anhydrase 9 (CA-9). These pathways enable neoangiogenesis and anaerobic metabolism, providing mechanisms for tumour invasiveness and survival. The degree of tissue hypoxia in tumours can be measured indirectly using these markers or imaging modalities, though these results can be non-specific (11). Multiple subsequent studies investigating HNSCC patients receiving radiation have now correlated the presence of these markers with poorer outcomes. Nordsmark *et al.* utilised electrodes to measure tumour pO_2 levels in HNSCC patients as an indirect marker of tissue hypoxia and found significant correlation between higher levels of tumour hypoxia pre-radiotherapy and higher rates of loco-regional failure (P=0.01), reduced disease-free survival (P=0.005) and survival (P=0.02). (13).

Koukourakis *et al.* (21) found that normal tissue does not express HIF-1a and HIF-2a and that HNSCC tumour cells with higher levels of these proteins had significantly greater VEGF expression and microvessel density. Overexpression of HIF1a and HIF2a was linked with incomplete response to chemoradiotherapy, poorer disease-free survival and overall survival, though these results were no longer statistically significant when subjected to multivariate analysis in which only HIF2a status remained an independent prognostic factor of overall survival (21,22). In a study by Beasley *et al.* (23), expression of CA-9 was measured in three cell lines of HNSCC tumour samples, and shown to be upregulated in peri-necrotic areas surrounding tumour tissue, with levels correlating to the degree of necrosis, and indirectly hypoxia. In a further study by Koukourakis *et al.*, which compared the expression of HIFs in normal head and neck mucosa to samples from 75 patients with locally advanced HNSCC, the levels of expression of HIF-1a and CA-9 of were significantly associated with poor disease-free survival, and overall survival for HIF-1a for patients receiving platinum-based chemoradiotherapy (21). In a 2012 study of 256 primary surgical patients with oral squamous cell carcinoma, Lin *et al.* showed a significant correlation between EPOR overexpression and advanced T stage (P<0.001), advanced TNM stage (P<0.001), and positive N classification (P=0.001). These results however were not demonstrable when performing multivariate

Table 1 Outcome measures of clinical trials

Study identifier	Number of patients (n)	Outcome measures		Risk of disease-associated death	Risk of overall death
		Loco-regional progression	Locoregional progression-free survival		
Henke *et al.* (25)	356	RR 1.69 (P=0.007)*	RR 1.62 (P=0.0008)*	–	RR 1.39 (P=0.02)*
RTOG 99-03 (26)	148	HR 1.33 (95% CI, 0.79–2.25) (P=0.56)	HR 1.26 (95% CI, 0.80–1.99)	–	HR 1.26 (95% CI, 0.77–2.06)
DAHANCA 10 (10)	522	HR 1.53 (95% CI, 1.16–2.02)	–	HR 1.43 (95% CI, 1.08–1.90)	HR 1.30 (95% CI, 1.02–1.64)
Hoskin *et al.* (27)	301	HR 0.94 (95% CI, 0.64–1.38) (P=0.740)	HR 1.04 (95% CI, 0.77–1.41) (P=0.791)	–	HR 1.04 (95% CI, 0.75–1.43) (P=0.823)

*, statistical significance. RR, relative risk; HR, hazard ratio; CI, confidence interval.

analysis (24).

Use of ESAs in HNSCC patients

Strong evidence linking anaemia with poorer locoregional control and overall survival in HNSCC has led researchers to pursue therapies which may improve haemoglobin levels. Despite correcting haemoglobin levels, the use of ESAs in HNSCC patients has failed to demonstrate an improvement in disease free survival or overall survival, see *Table 1* (10,25-27).

Henke *et al.* (25) performed a double-blinded, multicentre randomised control trial evaluating 351 HNSCC patients using epoetin beta to target haemoglobin levels >14 dg/L in women and >15 dg/L in men. Their cohort included both those receiving primary radiotherapy and post-surgical adjuvant radiotherapy for patients with advanced disease. Patients receiving epoetin beta had a significantly increased risk of disease progression (RR 1.69, P=0.07) and death (RR 1.39, P=0.02) though in a pooled Kaplan-Meier analysis for locoregional progression free survival, patients with complete surgical resection showed no significant difference. This result was potentially confounded by a difference in smoking rates between treatment (66%) and control (53%) groups, but the study was otherwise well-matched in potential confounders. The RTOG 99-03 (26) trial included mildly anaemic patients receiving definitive radiotherapy, excluding those with primary surgery or surgery with planned adjuvant radiotherapy. They excluded patients with haemoglobin values <9 or >13.5 g/dL in males and >12.5 g/dL in females. The study was terminated early following the release of the Henke trial showing the potentially detrimental effect of ESAs. Interim results of the RTOG 99-03 trial were equivocal, with no significant difference found in either locoregional control or survival. Caution must be taken in interpreting these results as the data was insufficiently powered to detect either beneficial or detrimental outcomes at this stage, and they conclude only that the results of the combined studies indicate that there is no indication for moderately anaemic patients with intended curative therapy to receive ESAs. The DAHANCA 10 (10) study evaluated the role of darbepoetin in primary RT patients with HNSCC. This randomised study excluded patients with prior surgical management. Recruitment was halted prematurely following a planned interim analysis which showed a trend towards poor outcomes amongst the darbepoetin group. Groups had no significant differences in baseline characteristics, and a total of 522 out of a planned 600 patients were included in the analysis. Darbepoetin alfa caused significantly worse outcomes for locoregional recurrence (HR 1.53; 95% CI: 1.16–2.02), disease-specific death (HR 1.43; 95% CI: 1.08–1.90) and event-free (HR 1.36; 95% CI: 1.09–1.69) and overall survival (HR 1.30; 95% CI: 1.02–1.64). In a Cox proportional hazards analysis of variables including T-status, nodal status, gender, performance status, smoking, HPV/p16 status and treatment with darbepoetin, controlled for tumour site, researchers demonstrated that the use of darbepoetin was associated with a higher risk of death (HR 1.30; 95% CI: 1.03–1.65) and locoregional recurrence (HR 1.51; 95% CI: 1.15–1.99) than smoking [HR 1.25, (95% CI: 1.01–1.55) and HR 1.32, (95% CI: 1.03–1.69) respectively]. In an open-label trial, Hoskin *et al.* (27) randomised 301 patients to standardised primary radiotherapy plus or minus epoetin alfa. It was insufficiently powered to detect its intended primary outcome (local disease-free survival)

and suffered from a high drop-out rate, with only 37% of its intended population studied until completion of the intended 5-year period. They conclude a neutral effect, with no significant difference in outcomes for disease-free survival, overall survival, cancer-treatment related anaemia or fatigue symptoms between groups. This study may also have inherent bias, being supported by a pharmaceutical company which produces epoetin alfa.

Conclusions and future directions

Despite a lack of research investigating surgical cohorts with HNSCC, the clear trend towards early locoregional failure and mortality amongst patients with advanced HNSCC receiving primary curative-intent radiotherapy on ESA therapy is suggestive of their relative contraindication. Several good quality randomised controlled trials have detected significant differences in rates of locoregional recurrence and overall survival. These studies and the issuing of a black-box warning by the FDA should alert clinicians to this risk. Future research aimed at stratifying the risk for surgical patients may be of benefit in early disease, when the risks are less well documented.

Acknowledgments

Thanks to Dr. Ben Chua for his assistance and expertise in contributing to the production of this article.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://www.theajo.com/article/view/10.21037/ajo-21-21/rc

Peer Review File: Available at https://www.theajo.com/article/view/10.21037/ajo-21-21/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://www.theajo.com/article/view/10.21037/ajo-21-21/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Australia CC. Skin cancer incidence and mortality Sydney: Cancer Council Australia; 2020. Available online: https://wiki.cancer.org.au/skincancerstats/Skin_cancer_incidence_and_mortality
2. Welfare AIoHa. Cancer data in Australia 2020. Available online: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation
3. Caro JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001;91:2214-21.
4. Baumeister P, Rauch J, Jacobi C, et al. Impact of comorbidity and anemia in patients with oropharyngeal cancer primarily treated with surgery in the human papillomavirus era. Head Neck 2017;39:7-16.
5. Rockwell S, Dobrucki IT, Kim EY, et al. Hypoxia and radiation therapy: past history, ongoing research, and future promise. Curr Mol Med 2009;9:442-58.
6. Horsman MR, Overgaard J. The impact of hypoxia and its modification of the outcome of radiotherapy. J Radiat Res 2016;57 Suppl 1:i90-8.
7. Littlewood TJ. The impact of hemoglobin levels on treatment outcomes in patients with cancer. Semin Oncol 2001;28:49-53.
8. Lutterbach J, Guttenberger R. Anemia is associated with decreased local control of surgically treated squamous cell carcinomas of the glottic larynx. Int J Radiat Oncol Biol Phys 2000;48:1345-50.
9. Lazzari G, Silvano G. From Anemia to Erythropoietin Resistance in Head and Neck Squamous Cell Carcinoma Treatment: A Carousel Driven by Hypoxia. Onco Targets Ther 2020;13:841-51.
10. Overgaard J, Hoff CM, Hansen HS, et al. DAHANCA 10 - Effect of darbepoetin alfa and radiotherapy in the

treatment of squamous cell carcinoma of the head and neck. A multicenter, open-label, randomized, phase 3 trial by the Danish head and neck cancer group. Radiother Oncol 2018;127:12-9.
11. Bredell MG, Ernst J, El-Kochairi I, et al. Current relevance of hypoxia in head and neck cancer. Oncotarget 2016;7:50781-804.
12. Kliger AS, Fishbane S, Finkelstein FO. Erythropoietic stimulating agents and quality of a patient's life: individualizing anemia treatment. Clin J Am Soc Nephrol 2012;7:354-7.
13. Nordsmark M, Overgaard J. A confirmatory prognostic study on oxygenation status and loco-regional control in advanced head and neck squamous cell carcinoma treated by radiation therapy. Radiother Oncol 2000;57:39-43.
14. Bohlius J, Tonia T, Nüesch E, et al. Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: systematic review and meta-analyses of published and unpublished data. Br J Cancer 2014;111:33-45.
15. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. Lancet 2009;373:1532-42.
16. Collister D, Komenda P, Hiebert B, et al. The Effect of Erythropoietin-Stimulating Agents on Health-Related Quality of Life in Anemia of Chronic Kidney Disease: A Systematic Review and Meta-analysis. Ann Intern Med 2016;164:472-8.
17. FDA. Information on Erythropoiesis-Stimulating Agents (ESA) Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp) 2017. Available online: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin
18. Bohlius J, Bohlke K, Castelli R, et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol 2019;37:1336-51.
19. Wang H, Jiang H, Van De Gucht M, et al. Hypoxic Radioresistance: Can ROS Be the Key to Overcome It? Cancers (Basel) 2019;11:112.
20. Hedley BD, Allan AL, Xenocostas A. The role of erythropoietin and erythropoiesis-stimulating agents in tumor progression. Clin Cancer Res 2011;17:6373-80.
21. Koukourakis MI, Giatromanolaki A, Sivridis E, et al. Hypoxia-inducible factor (HIF1A and HIF2A), angiogenesis, and chemoradiotherapy outcome of squamous cell head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;53:1192-202.
22. Koukourakis MI, Giatromanolaki A, Sivridis E, et al. Hypoxia-regulated carbonic anhydrase-9 (CA9) relates to poor vascularization and resistance of squamous cell head and neck cancer to chemoradiotherapy. Clin Cancer Res 2001;7:3399-403.
23. Beasley NJ, Wykoff CC, Watson PH, et al. Carbonic anhydrase IX, an endogenous hypoxia marker, expression in head and neck squamous cell carcinoma and its relationship to hypoxia, necrosis, and microvessel density. Cancer Res 2001;61:5262-7.
24. Lin YT, Chuang HC, Chen CH, et al. Clinical significance of erythropoietin receptor expression in oral squamous cell carcinoma. BMC Cancer 2012;12:194.
25. Henke M, Laszig R, Rübe C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255-60.
26. Machtay M, Pajak TF, Suntharalingam M, et al. Radiotherapy with or without erythropoietin for anemic patients with head and neck cancer: a randomized trial of the Radiation Therapy Oncology Group (RTOG 99-03). Int J Radiat Oncol Biol Phys 2007;69:1008-17.
27. Hoskin PJ, Robinson M, Slevin N, et al. Effect of epoetin alfa on survival and cancer treatment-related anemia and fatigue in patients receiving radical radiotherapy with curative intent for head and neck cancer. J Clin Oncol 2009;27:5751-6.

doi: 10.21037/ajo-21-21
Cite this article as: Rogers ML, Rughani M. The safety of erythropoietin stimulating agents in surgical patients with head and neck squamous cell carcinoma—a narrative review. Aust J Otolaryngol 2022;5:26.