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A comparative study of the iron status of patients with oesophageal adenocarcinoma to determine suitability for a clinical trial of iron chelation therapy

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ABSTRACT

INTRODUCTION The incidence of oesophageal adenocarcinoma (OAC) is rising dramatically and overall survival remains extremely poor. Iron has been shown to potentiate tumourigenesis in OAC, and iron chelation therapy demonstrates promise in vivo as an adjunct to neoadjuvant and palliative chemotherapy. OAC, however, has traditionally been associated with iron deficiency anaemia. The aim of this study was therefore to formally quantify the iron status of OAC patients in order to guide the design of future clinical trials involving iron chelation therapy.

METHODS Demographic and cancer specific data were collected prospectively from all patients presenting with OAC and gastric adenocarcinoma (GAC). Patients had haemoglobin, serum iron, serum ferritin and serum transferrin receptor (sTfR) levels measured to assess systemic iron status. In addition, the sTfR/log ferritin (sTfR-F) index was calculated.

RESULTS Average haemoglobin, serum iron, serum ferritin, sTfR and sTfR-F index values for all patients presenting with OAC were within normal sex specific reference ranges. No statistical difference in iron status was observed between OAC patients presenting with resectable and advanced OAC. Patients with OAC are relatively iron replete compared with those presenting with GAC. Iron parameters were not significantly altered by standard neoadjuvant chemotherapy.

CONCLUSIONS Patients presenting with resectable or advanced OAC could be considered as candidates for a clinical trial of iron chelation therapy as an addition to standard neoadjuvant or palliative treatments.

KEYWORDS

Oesophageal adenocarcinoma – Chelation – Deferasirox – Anaemia

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Carcinoma of the oesophagus is a significant cause of morbidity and mortality. In 2008 alone there were approximately 482,300 new cases worldwide and the disease was responsible for over 400,000 deaths.[1] The incidence of oesophageal adenocarcinoma (OAC) in particular has risen dramatically over recent decades.[2]

The outlook for those diagnosed with OAC remains dismal; overall five-year survival rates are around 10%.[2] Most patients have advanced disease on presentation and only around 25% can undergo potentially curative surgery.[3]

Chemotherapy plays a significant role in the management of OAC, be it as an adjunct to surgery for those with resectable disease or in the palliative setting. Response to standard therapy regimens, however, remains variable.[3] The development and application of new agents that improve the response to chemotherapy would therefore be invaluable.

There is an emerging body of evidence implicating iron in the malignant progression of gastrointestinal cancer.[4,5] Of note, a high dietary intake of haem iron has been shown to correlate with increased OAC risk in humans.[6,7] Likewise, excess systemic iron has been shown to exacerbate oesophageal tumourigenesis in animal models.[8] The increased accumulation of intracellular iron has also been demonstrated along the progression of Barrett's metaplasia to OAC.[9] These associations are not entirely surprising as iron is essential for a number of key cellular processes including synthesis of deoxyribonucleic acid, adenosine triphosphate generation and cell cycle progression, all of which are increased in cancer.[10]

With this in mind, there is now evidence suggesting that iron chelators (agents that bind iron, used currently in diseases associated with systemic iron overload such as

hereditary haemochromatosis and beta thalassaemia) could act as potent antineoplastic and/or chemosensitising agents.[11,12] Of note, the clinically established iron chelator desferrioxamine has been shown to possess antineoplastic properties in a small clinical trial of neuroblastoma patients.[13] Furthermore, the advent of orally active, licensed chelating agents such as deferasirox (Exjade®; Novartis, Basel, Switzerland), has revolutionised iron chelation therapy with the elimination of lengthy parenteral infusions and associated poor adherence.[14] It has been demonstrated recently that deferasirox possesses significant antineoplastic activity against OAC cells both in vitro and in vivo, and, as such, the drug is well placed to be considered for a clinical trial in this setting.[15,16]

Iron chelators may, however, have the potential to induce anaemia, which is commonly associated with gastrointestinal cancers.[17] Previous studies in oesophageal cancer have estimated the incidence of anaemia on presentation to range from 20% to 45%.[18,19] Clearly, any benefit seen for patients treated with iron chelation therapy in terms of antineoplastic activity or chemosensitisation would be substantially negated by the development of iron deficiency and/or anaemia and its associated side effects.

The aim of this study was therefore to characterise the iron status of patients presenting with OAC to determine the suitability of such a cohort to be included in a future clinical trial of iron chelation therapy. Haemoglobin (Hb) concentration and iron status (including the transferrin/ferritin ratio) of OAC patients was compared with standard, sex specific reference ranges and a cohort of gastric adenocarcinoma (GAC) patients (representing a group of patients classically associated with chronic blood loss secondary to bleeding into the gastrointestinal tract).

Methods

All data were collated prospectively over a two-year period (2008–2010) from a tertiary hospital offering a specialist upper gastrointestinal cancer resectional service. Inclusion criteria were all patients presenting with OAC (including Siewert types I, II and III) and all patients presenting with gastric adenocarcinoma. All patients had histologically proven malignancy. Patient demographics were recorded and blood samples taken at presentation for haematological and biochemical iron parameters. Patients were followed through the normal multidisciplinary team cancer evaluation and treatment pathways. Tumour characteristics and treatment outcomes were recorded. All haematological and biochemical quantification was performed on automated high throughput analysers at the host institution's department of haematology and biochemistry. Data were analysed using two-tailed t-tests and statistical significance was declared at a p-value of 0.05. The study received approval from the local regional ethics committee.

Data collected

Data collected included: patient age, sex, tumour characteristics (radiological and endoscopic location, histological diagnosis), type of treatment (neoadjuvant, adjuvant or palliative chemotherapy, resection or non-operative treatment), pathological tumour staging, and haematological and biochemical iron parameters (Hb, serum iron, serum ferritin and soluble transferrin receptor [sTfR] concentration). The sTfR-F index was derived by sTfR/log ferritin.

The normal reference ranges used were:

- Hb: male 135–180g/l, female 115–165g/l
- serum ferritin: male 18–360μg/l, female 10–320μg/l
- serum iron: male 10–32μmol/l, female 5–30μmol/l
- sTfR: male and female 2.0–3.6mg/l
- sTfR-F index: male and female >1.8 equates to storage iron depletion, >2.2 to iron deficient erythropoiesis and >2.8 to iron deficiency anaemia[20]

Results

Data were available for all patients presenting with OAC (n=71) and GAC (n=51) (resected and unresected cases). The mean age of patients with OAC was 65.5 years and for GAC patients it was 73.0 years. Patients with OAC were significantly younger than those with GAC (p=0.0004).

Fifty-five OAC patients (78%) were male. The mean Hb for male OAC patients was 13.8g/dl and for female patients it was 11.8g/dl. The mean serum ferritin was 265μg/l and 91μg/l for male and female patients respectively, and the mean levels for serum iron were 13.4μmol/l and 12.3μmol/l respectively. The mean sTfR was 2.64mg/l for male and 2.92mg/l for female patients. The mean sTfR-F index values were 1.35 for male and 1.72 for female patients. This is well within normal limits for male and within the upper limit of normal for female patients.

Resectable OAC vs advanced OAC

No significant differences were observed between resectable and advanced OAC at presentation (Table 1).

Iron status before and after neoadjuvant chemotherapy for OAC

In order to assess the impact of standard chemotherapy on systemic iron and Hb concentrations, data were collected before and after neoadjuvant chemotherapy for those allocated to it following multidisciplinary team discussion. The regime of epirubicin, cisplatin and fluorouracil/capecitabine (ECX) is typically used in our institution.

A full iron profile was available for 11 patients in total who underwent neoadjuvant chemotherapy with ECX. A significant fall in mean Hb concentration was evident following neoadjuvant treatment (13.9g/dl to 12.5g/dl for pre and post-treatment respectively, p=0.019) although the difference in mean values was just 1.4g/dl. No significant difference was observed prior to and following neoadjuvant chemotherapy in mean serum ferritin (161μg/l and 280μg/l, p=0.34), serum iron (13.1μmol/l and 13.8μmol/l, p=0.81) or sTfR (2.63mg/l and 2.79mg/l, p=0.33). Despite a significant drop in mean Hb before and after chemotherapy, no change in mean sTfR-F index value was seen (1.47 vs 1.43, p=0.89).

Table 1 Iron parameters by comparison

	Haemoglobin in g/dl (SD)			Ferritin in µg/l (SD)			Serum iron in µmol/l (SD)			sTfR in mg/l (SD)			sTfR-F index		
	OAC	GAC	*p*-value	OAC	GAC	*p*-value	OAC	GAC	*p*-value	OAC	GAC	*p*-value	OAC	GAC	*p*-value
OAC resection vs GAC resection	13.2 (1.8)	12.4 (2.1)	**0.042**	236 (278)	141 (258)	0.18	13.6 (5)	12.5 (6.2)	0.44	2.78 (0.52)	2.87 (0.38)	0.48	1.50 (0.78)	1.84 (0.94)	0.13
Advanced OAC vs advanced GAC	13.6 (2.4)	11.8 (2.2)	**0.028**	317 (258)	219 (319)	0.53	11.3 (4.3)	13.1 (4.2)	**0.50**	2.35 (0.35)	2.65 (0.57)	0.25	1.11 (0.50)	1.98 (1.39)	0.14
Resectable OAC vs advanced OAC	13.2 (1.8)	13.6 (2.4)	0.48	236 (278)	317 (258)	0.48	13.6 (5)	11.3 (4.3)	0.29	2.78 (0.52)	2.35 (0.35)	0.44	1.50 (0.78)	1.11 (0.50)	0.22

Hb = haemoglobin; SD = standard deviation; sTfR = soluble transferrin receptor; sTfR-F = sTfR/log ferritin; OAC = oesophageal adenocarcinoma; GAC = gastric adenocarcinoma

OAC resection vs GAC resection cohort

Fifty-two (39 male and 13 female) OAC patients (67%) had an oesophagectomy and 34 (24 male and 10 female) GAC patients (67%) underwent a radical gastrectomy. The mean age of patients undergoing an oesophagectomy was 65.1 years. This was significantly younger than gastrectomy patients at 71.5 years (p=0.0039).

At initial presentation, the mean Hb level of patients who subsequently progressed to potentially curative surgery was significantly higher in those undergoing a radical oesophagectomy (13.2g/dl vs 12.4g/dl for oesophageal and gastric resections respectively, p=0.042). There was a trend towards mean serum ferritin levels being higher in OAC than in GAC patients. However, the difference was not statistically significant (236µg/l vs 141µg/l for oesophageal and gastric resections respectively, p=0.18). No difference was observed between the two cohorts for serum iron and sTfR concentrations. Although the mean sTfR-F index values were not significantly different between the two cohorts, the mean value for those with GAC was at the upper limit of normal (1.5 vs 1.84 for oesophageal and gastric resections, p=0.13).

Advanced OAC vs advanced GAC

Twenty-six patients (33%) presenting with OAC were subsequently found to have unresectable disease by radiological staging compared with seventeen patients (33%) with GAC. The mean Hb concentration was the only parameter to reach statistical significance between the two groups (13.6g/dl vs 11.8g/dl for OAC and GAC patients respectively, p=0.028). The mean sTfR-F index value for patients with GAC was well into the range denoting depletion of stored iron (1.11 vs 1.98, p=0.14).

Discussion

The aim of this study was to investigate the iron status of patients presenting with OAC to determine the suitability of such a cohort to be included in a future clinical trial of iron chelation therapy as an adjunct to current treatment modalities. In this relatively small, single centre study, markers of systemic iron status (Hb, serum iron, serum ferritin, sTfR and sTfR-F index) were all found to be within normal sex specific reference limits at initial presentation. Furthermore, patients presenting with advanced disease (and therefore only offered palliative chemotherapy or best supportive care) were not significantly iron depleted compared with patients with localised disease who were suitable for potentially curative resection.

A statistically significant decrease in Hb was seen in patients undergoing neoadjuvant chemotherapy with ECX (13.9g/dl to 12.5g/dl, p=0.019). This is a smaller decrease than that documented in a previous study by Voelter *et al*, who noted a significant reduction following chemotherapy of 2.9g/dl.[21] However, Voelter *et al* focused solely on Hb levels and did not measure any of the other iron parameters assessed here. This is an important omission as in our study, despite the decrease in Hb, there were no differences observed in any of the other parameters measured, including sTfR-F index.

Unlike serum ferritin as a marker of systemic iron store, the sTfR-F index is independent of inflammation. It has been shown to distinguish accurately between iron replete and iron deplete anaemic patients, and also to detect iron deficiency without anaemia.[21] Neoadjuvant treatment for OAC, therefore, does not appear to affect iron status significantly, indicating that patients are unlikely to become more anaemic with the addition of an iron chelating agent to existing chemotherapeutic regimes.

The iron status of patients with early and advanced OAC compared favourably with the iron status of patients presenting with similarly staged GAC. Patients with OAC had a significantly higher Hb concentration than those presenting with GAC. Patients with advanced GAC also had evidence of inadequate iron stores with a mean sTfR-F index above 1.8. This may reflect that patients with GAC are more inclined to bleed into the gastrointestinal tract than OAC patients or may have a greater tumour surface area from which to bleed.

This study is limited by inclusion of a relatively small number of patients from a single tertiary upper gastrointestinal cancer resectional centre. This is in part likely to

explain the percentage of patients presenting with resectable OAC (67%), which is much higher than expected. This limitation has been acknowledged in previous studies.[19] This, in turn, may have influenced the average blood parameter values for the overall OAC cohort.

In vitro and in vivo evidence suggests iron chelation to be a promising and safe adjunct to oesophageal cancer treatment.[17] Importantly, the orally administered chelator, deferasirox, has been shown to reduce tumour burden significantly in a murine model of OAC without any effect on either Hb or systemic iron levels. This drug has shown promise in a number of other cancers and may possess antineoplastic effects that are mediated through a number of pathways in addition to iron chelation alone.[18]

Conclusions

This study demonstrates that patients presenting with OAC are iron replete and would be suitable to enter a pilot trial of iron chelation therapy as an adjunct to standard treatment regimes. This approach could have a significant impact on tumour response rates to chemotherapy, both in the neoadjuvant and palliative settings, and could translate to improved clinical outcomes for patients with oesophageal and gastro-oesophageal junction cancers.

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