BJP British Journal of Pharmacology

DOI:10.1111/bph.12093
www.brjpharmacol.org

COMMENTARY

Iron chelation: a potential therapeutic strategy in oesophageal cancer

BD Keeler[1] and MJ Brookes[2]

[1]*Division of Gastrointestinal Surgery, Queen's Medical Centre, Nottingham, UK, and*
[2]*Gastroenterology Unit, Royal Wolverhampton NHS Trust, Wolverhampton, West Midlands, UK*

Correspondence
Dr Matthew James Brookes, Gastroenterology Unit, Royal Wolverhampton NHS Trust, Wednesfield Road, Wolverhampton WV10 OQP, UK.
E-mail: m.j.brookes@bham.ac.uk

Keywords
iron chelation; deferoxamine; deferasirox; anti-tumour agents; cell cycle

Received
29 October 2012
Revised
19 November 2012
Accepted
6 December 2012

Raised intracellular iron has been identified as a potential aetiological factor in the development of several epithelial malignancies, including those of the gastrointestinal tract. The mechanism behind this increase is thought to include disorders of iron uptake and storage. Several iron chelators have been identified as potential anti-tumour agents, with much work undertaken to ascertain the exact mode of action. Despite this, there is little known about the role that these drugs play in the cellular iron metabolism of oesophageal cancer. Consequently, the present study looks to review the relationship of two clinically important iron-chelating agents, deferoxamine and deferasirox, on cellular iron uptake and storage in oesophageal squamous and adenocarcinoma. This provides important evidence for the debate about the role these agents have in the clinical management of such tumours.

LINKED ARTICLE

This article is a commentary on Ford *et al.*, pp. 1316–1328 of this issue. To view this paper visit http://dx.doi.org/10.1111/bph.12045

Abbreviations

DFO, deferoxamine; PIH, pyridoxal isonicotinoyl hydrazone; TFR1, transferrin receptor 1

Iron is an essential trace element for mammalian life as it is involved in numerous cellular processes, including oxygen transport, oxidative phosphorylation, DNA synthesis and cell cycle progression (Kovacevic *et al.*, 2011). Numerous epidemiological, animal and *in vitro* studies have demonstrated a potential carcinogenic role for this metal in the development of several epithelial cancers (Brookes *et al.*, 2008). Several key reports have also identified that tumours cells may be lacking homeostatic mechanisms to regulate intracellular iron. In particular, oesophageal (Boult *et al.*, 2008) and colorectal cancers (Brookes *et al.*, 2008) have been shown to modify cellular expression of iron-related proteins, including transferrin receptor 1 (TFR1), ferritin and ferroportin 1, which are involved in iron storage or flux across a cell. The exact mechanism behind these changes is not well understood in oesophageal cancer, but it was recently shown that in colorectal adenocarcinoma, cells seem to lose the ability to appropriately sense intracellular iron levels. The abnormally high cellular iron in colorectal adenocarcinoma appears to occur through the effects of oncogenic products (c-myc) generated by the main carcinogenic pathway, Wnt signalling (Brookes *et al.*, 2008, Coombs *et al.*, 2012).

The concepts raised by such studies have drawn attention to the potential therapeutic applications of chelating iron in the treatment of cancer. The safe use of deferoxamine (DFO) has already been established in the treatment of disorders of systemic iron overload (Blatt and Stitely, 1987), and thus made such agents ideal for initial investigation of the anti-neoplastic properties of this drug class. Early work identified that DFO possessed potent anti-tumour activity *in vitro* (Blatt and Stitely, 1987), which prompted further evaluation of compounds with more potent chelating activity, oral bioavailability and lower costs. The pyridoxal isonicotinoyl hydrazone (PIH) class satisfied these requirements; hence, chelators in this class have also been extensively investigated showing a similar anti-tumour role (Richardson *et al.*, 1995). Subsequent evaluation of the relationship between the functional activity and chemical structure of the PIH class led to the development of the thiosemicarbazones (di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone; Dp44mT and 2-benzoylpyridine-4,4-dimethyl-3-thiosemicarbazone; Bp44mT) with potential for increased cytotoxic efficacy (Whitnall *et al.*, 2006). Ultimately, the proposed cytotoxic mechanism of action of these iron chelators is related to

inhibition of ribonucleotide reductase, an iron-containing enzyme that regulates DNA synthesis, (Richardson *et al*., 1995), resulting in reduced cellular proliferation, and also by impeding antioxidant protection and affecting apoptosis (Yu *et al*., 2012).

The anti-neoplastic properties of these agents have been demonstrated in a variety of tumour groups, but such a role has yet to be investigated in the treatment of gastrointestinal cancers. This body of evidence is now augmented by the work of Ford *et al*. (2012), who have demonstrated that using DFO, deferasirox or Dp44mT can have similar anti-neoplastic effects in both oesophageal adenocarcinoma and squamous cell carcinoma models. In a series of exciting experiments, the research group demonstrated that deferasirox lead to *in vitro* depletion of cellular iron, and inhibits oesophageal cancer growth *in vivo*. The depletion of intracellular iron stores appeared to be a product of limiting iron uptake into the cell (10–90% reduction dependent on agent) and increasing iron mobilization from intracellular stores (30–75% dependent on agent). A result of this iron depletion was to lead to cellular changes in iron transport machinery, with an up-regulation of the iron import protein TFR1 and down-regulation in the iron export protein ferroportin, suggesting an intact iron-regulatory protein pathway (Muckenthaler *et al*., 2008). The latter is an important finding, as it shows that these cells do not appear to have the abnormal iron homeostatic mechanisms seen in colorectal adenocarcinoma, which occurs through activated Wnt signalling (Brookes *et al*., 2008).

More importantly, Ford *et al*. also demonstrate a functional efficacy of these agents through reduced cellular viability, proliferation and enhanced chemosensitivity to standard cytotoxic agents. The use of tumour xenograft models were also used to show that low-dose deferasirox could inhibit tumour growth by up to 43% *in vivo*, through depletion of cellular iron. There were no adverse effects seen from the iron chelation in the host, and in particular, no evidence of anaemia or systemic iron depletion was found.

Based on the findings from this paper by Ford *et al*. deferasirox may have a therapeutic role in treating oesophageal cancer and potentially other epithelial cancers associated with disordered cellular iron metabolism. The exact mechanisms of the anti-cancer effects of deferasirox, beyond iron chelation, are still poorly understood. Interestingly, deferasirox has also been shown to be a potent inhibitor of Wnt signalling (Song *et al*., 2011), which may suggest potential for this agent in colorectal adenocarcinoma. This study may therefore open the door to similar studies in other epithelial malignancies.

The importance of this study perhaps lies in the increasing incidence and poor outcomes afforded to patients with oesophageal carcinoma. Despite recent improvements in detection and treatment, the overall survival of patients with oesophageal cancer remains lower than most solid tumours, with overall 5 years survival rates around 8% (CRUK, 2012). In addition to this, the tolerability of standard chemotherapeutic regimes to patients in either the neo-adjuvant or palliative setting is poor. It is also known that anaemia can complicate oesophageal cancer in up to 45% of cases (Melis *et al*., 2009; Tanswell *et al*., 2011), and the chemotherapeutic regimes used in cancer chemotherapy may exacerbate this anaemia. These factors combine to highlight why further advances in the management of oesophageal carcinoma are so desperately needed. The availability of an effective iron chelator, which is well tolerated, does not cause anaemia and can potentially have a positive impact on survival rates will be a welcome relief to patients with the disease.

Well-designed clinical trials of this and the newer iron chelators are now needed to determine the tolerability and clinical efficacy of these agents in oesophageal carcinoma. Further, *in vitro* and *in vivo* studies of these agents are likely to be needed to investigate their potential use in other epithelial cancers, in particular colorectal adenocarcinoma.

Conflict of interest

MJB has received travel support and research grants from Vifor International. BDK has no conflicts of interest to declare.

References

Blatt J, Stitely S (1987). Antineuroblastoma activity of desferoxamine in human cell lines. Cancer Res 47: 1749–1750.

Boult J, Roberts K, Brookes MJ, Hughes S, Bury JP, Cross SS *et al*. (2008). Overexpression of cellular iron import proteins is associated with malignant progression of esophageal adenocarcinoma. Clin Cancer Res 14: 379–387.

Brookes MJ, Boult J, Roberts K, Cooper BT, Hotchins NA, Matthews G *et al*. (2008). A role for iron in Wnt signalling. Oncogene 27: 966–975.

Cancer Research UK (CRUK) (2012). Oesophageal cancer statistics. Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oesophagus/ (accessed 22 October 2012).

Coombs GS, Schmitt AA, Canning CA, Alok A, Low ICC, Banerjee N *et al*. (2012). Modulation of Wnt/b-catenin signaling and proliferation by a ferrous iron chelator with therapeutic efficacy in genetically engineered mouse models of cancer. Oncogene 31: 213–225.

Ford S, Obeidy P, Lovejoy DB, Bedford M, Nichols L, Chadwick C *et al*. (2012). Deferasirox (ICL670A) effectively inhibits oesophageal cancer growth *in vitro* and *in vivo*. Br J Pharmacol 168: 1316–1328.

Kovacevic Z, Kalinowski DS, Lovejoy DB, Yu Y, Suryo Rahmanto Y, Sharpe PC *et al*. (2011). The medicinal chemistry of novel iron chelators for the treatment of cancer. Curr Top Med Chem 11: 483–499.

Melis M, McLoughlin JM, Dean EM, Siegel EM, Weber JM, Shah N *et al*. (2009). Correlations between neoadjuvant treatment, anemia, and perioperative complications in patients undergoing esophagectomy for cancer. J Surg Res 153: 114–120.

Muckenthaler MU, Galy B, Hentze MW (2008). Systemic iron homeostasis and the iron-responsive element/iron-regulatory protein (IRE/IRP) regulatory network. Annu Rev Nutr 28: 197–213.

Richardson DR, Tran EH, Ponka P (1995). The potential of iron chelators of the pyridoxal isonicotinoyl hydrazone class as effective antiproliferative agents. Blood 86: 4295–4306.

Song S, Christova T, Perusini S, Alizadeh S, Bao RY, Miller BW *et al*. (2011). Wnt inhibitor screen reveals iron dependence of β-catenin signaling in cancers. Cancer Res 71: 7628–7639.

Tanswell I, Steed H, Butterworth J, Townson G (2011). Anaemia is of prognostic significance in patients with oesophageal adenocarcinoma. J R Coll Physicians Edinb 41: 206–210.

Whitnall M, Howard J, Ponka P, Richardson DR (2006). A class of iron chelators with a wide spectrum of potent antitumor activity that overcomes resistance to chemotherapeutics. Proc Natl Acad Sci U S A 103: 14901–14906.

Yu Y, Rahmanto YS, Richardson DR (2012). Bp44mT: an orally active iron chelator of the thiosemicarbazone class with potent anti-tumour efficacy. Br J Pharmacol 165: 148–166.