European Journal of Cancer (2012) 48, 2117–2124

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Evaluating the efficacy of statins and ACE-inhibitors in reducing gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies

Linda J. Wedlake [a], Foteini Silia [b], Barbara Benton [b], Amyn Lalji [b], Karen Thomas [c], David P. Dearnaley [d,e], Peter Blake [f], Diana Tait [b], Vincent S. Khoo [d], H. Jervoise N. Andreyev [b,*]

[a] *Department of Nutrition and Dietetics, The Royal Marsden NHS Foundation Trust, London, UK*
[b] *The GI Unit, The Royal Marsden NHS Foundation Trust, London, UK*
[c] *Department of Computing, The Royal Marsden NHS Foundation Trust, London, UK*
[d] *Department of Urology, The Royal Marsden NHS Foundation Trust, London, UK*
[e] *The Institute of Cancer Research, UK*
[f] *Department of Gynaecology, The Royal Marsden NHS Foundation Trust, London, UK*

Received 2 September 2011; received in revised form 12 November 2011; accepted 11 December 2011
Available online 3 March 2012

KEYWORDS
Pelvic radiotherapy
Normal tissue toxicity
Gastrointestinal
Statins
Hypertension
ACE inhibitors

Abstract ***Introduction:*** 3-Hydroxy-methylglutaryl coenzyme-A reductase inhibitors (statins) improve survival following pelvic irradiation for cancer. Large studies suggest that patients with hypertension may have reduced gastrointestinal (GI) toxicity. Animal data suggest that statins and ACE inhibitors (ACEi) may protect against normal tissue injury. Their efficacy in humans has not been reported.

Aimslmethods: To evaluate the impact of statins and ACEi on normal tissue toxicity during radical pelvic radiotherapy. GI symptomatology was recorded prospectively before radiotherapy, weekly during treatment and 1 year later using the Inflammatory Bowel Disease Questionnaire – Bowel (IBDQ-B) subset. Cumulative acute toxicity (IBDQ-B AUC) and worst score were determined. Dose, brand and duration of statin and/or ACEi usage were obtained from General Practitioners.

Results: Of 308 patients recruited, 237 had evaluable acute drug and toxicity data and 164 had data at 1 year. Acutely, 38 patients (16%) were taking statins, 39 patients (16.5%) were taking ACEi and 18 patients (7.6%) were taking statin + ACEi. Mean changes in acute scores were 7.3 points (non-statin users), 7.3 (non-ACEi users) and 7.0 (non-statin + ACEi users) compared to 4.8 points (statin users), 5.0 points (ACEi users) and 4.9 points (statin + ACEi users).

* *Corresponding author:* Address: The GI Unit, Department of Medicine, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK. Tel.: +44 207 811 8216; fax: +44 207 811 8107.
E-mail address: J@andreyev.demon.co.uk (H. Jervoise N. Andreyev).

doi:10.1016/j.ejca.2011.12.034

Statin use ($p = 0.04$) and combined statin + ACEi use ($p = 0.008$) were associated with reduced acute IBDQ-B AUC after controlling for baseline scores (ANOVA). At 1 year, users maintained higher IBDQ-B scores than non-users in all user subgroups.

Conclusion: Use of statin or statin + ACEi medication during radical pelvic radiotherapy significantly reduces acute gastrointestinal symptoms scores and also appears to provide longer-term sustained protection.

1. Introduction

Clinical evidence suggests that the cholesterol-lowering agents, 3-hydroxy-methylglutaryl coenzyme-A reductase inhibitors, 'statins', improve outcomes following therapeutic irradiation for pelvic cancers. Of three studies conducted between 2009 and 2011 in 3340 prostate cancer patients of whom 23–27% of patients reported using statins, two studies[1,2] ($n = 2372$) showed significant improvements in PSA relapse free survival and freedom from biochemical failure respectively in statin users versus non-users whilst a third study[3] ($n = 968$) showed no effect. In a smaller study of 349 rectal cancer patients[4] of whom 9% were reportedly taking statins, a significantly improved complete pathological response rate following radiotherapy was reported in statin users and in a further study of 286 bladder cancer patients[5] (12% reporting statin use) improved local control was reported in statin users on univariate (but not multivariate) analysis. The mechanism of action is attributed to enhanced sensitisation of tumour cells to cytocidal irradiation.

However, statins may also be protective for normal tissues. The mechanism of action is (at least partly) via blockade of the enzyme HMGCoA reductase and thus a reduced cellular pool of mevalonate derived isoprenoid intermediates required for the activation of Rho (ras homologous) GTPases and consequently the Rho/ROCK (Rho-associated kinase) signalling pathway. Impedance results in downstream inhibition of pro-fibrotic and pro-inflammatory cytokines, attenuation of mediators of vascular damage and failure to respond to cytokine or growth factor mediated stimulation. *In-vitro* investigations have clearly demonstrated the anti-inflammatory,[6] anti-fibrotic[7,8] and anti-thrombotic[7,8] potential of pravastatin in irradiated human cell lines whilst low dose lovastatin[9] has been shown to be radio-protective in human endothelial cells. *In-vivo* investigations of the efficacy of pravastatin[8,10] simvastatin[11] and lovastatin[12] in animal models employing exteriorised irradiated small bowel[8,10,11] and total body irradiation[12] have demonstrated reversal of established intestinal fibrosis,[8] mitigation of delayed intestinal enteropathy,[10] significantly reduced ileal injury after fractionated treatment[11] and attenuated expression of pro-fibrotic, inflammatory and thrombotic markers in a tissue and time dependent manner.[12] No clinical studies have yet reported on these topics.

ACE (angiotensin I-converting enzyme) inhibitors (ACEi) may also have a role in the reduction of radiation-induced toxicity. These anti-hypertensive agents block enzymatic conversion of angiotensin I to angiotensin II playing a critical role in blood pressure homoeostasis. Animal studies focussing on the protective effects of ACEi in lung tissue yielded promising results.[13] One study[14] has addressed the efficacy of ACEi and gastrointestinal toxicity but showed no benefit. In lung patients, two clinical studies (10 years apart) have been conducted, one[15] showed a clear benefit in 14% of the ACEi users ($n = 146$) in preventing radiation-induced lung injury in multivariate analysis, whilst the earlier study did not.[16] With respect to gastrointestinal toxicity, five clinical studies[17–22] conducted between 2004 and 2011 amounting to $n = 4855$ prostate cancer patients have included an analysis of the impact of presence of hypertension on normal tissue toxicity with three studies[17,21,22] reporting a protective effect. Only one of these studies – from our unit – included patients treated for non-urological cancers and this showed reduced toxicity in hypertensive patients irrespective of tumour site.[22]

The most likely reason for the paradoxical finding of reduced toxicity in hypertensive patients comes from the use of anti-hypertensive medication. In the five studies[17–21] referenced above, 22–46% of patients reported hypertension as a co-morbidity before starting radiotherapy although only one study[20] captured data on whether anti-hypertensive medication was being used. Favourable effects of the presence of hypertension in three studies[17,20,21] ($n = 3103$ patients) included improved urinary function (with a trend towards reduced risk of proctitis),[17] protection from diarrhoea[20] and reduced risk of grade 2 or greater gastrointestinal toxicity.[21] In the remaining two studies, one ($n = 1010$) found no effect on late rectal toxicity[19] and the other[18] ($n = 742$) reported that the presence of hypertension was predictive for late grade 2 gastrointestinal toxicity.

We aimed to determine whether statins and ACEi reduce normal tissue toxicity during therapeutic pelvic radiotherapy. Data were used from a mixed cohort of 308 pelvic radiotherapy patients in whom gastrointestinal toxicity outcomes had been previously captured prospectively[22] and the impact of individual statin and