Clinical Oncology 28 (2016) 116–139

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Combination of Novel Agents with Radiotherapy to Treat Rectal Cancer

T.A. Greenhalgh, C. Dearman, R.A. Sharma

NIHR Oxford Biomedical Research Centre, CRUK-MRC Institute for Radiation Oncology, Department of Oncology, University of Oxford, Oxford, UK

Received 9 August 2015; received in revised form 25 October 2015; accepted 26 October 2015

Abstract

Neoadjuvant chemoradiotherapy with fluoropyrimidines is an established treatment in the management of locally advanced rectal cancer. There has been a great deal of research into improving patient outcomes by modifying this regimen by the addition of further radiosensitising agents. One of the difficulties in advancing new combination therapies has been lack of consensus on which surrogate measures best reflect clinically important outcomes. Here we review combinations of the cytotoxic, biological and other agents currently under scrutiny to improve clinical outcomes for patients with colorectal cancer. We also discuss advances in biomarkers that may ultimately result in an ability to tailor neoadjuvant chemoradiotherapy regimens to the somatic gene profile of individual patients.

Key words: Cetuximab; fluorouracil; irinotecan; oxaliplatin; radiosensitisation

Statement of Search Strategies Used and Sources of Information

Data for this review article were identified through a search of Embase, Medline and Web of Science. The following terms were used together with any derivatives: colorectal cancer, radiosensitiser, radiotherapy, radiation, chemoradiotherapy, chemotherapy, drug therapy, novel agent, targeted agent, biological agent, bevacizumab, aflibercept, cetuximab and panitumumab. Only articles published in English were selected. The search also included the reference list for these articles and selected additional articles judged to be relevant.

Introduction

Although the original demonstration of significant radiosensitisation by a chemotherapeutic agent in combination with radiotherapy for rectal cancer was in the adjuvant setting [1], clinical practice has moved away from adjuvant radiotherapy to the current practice of neoadjuvant chemoradiotherapy (CRT) [2,3]. The combination of neoadjuvant radiotherapy with a fluoropyrimidine is now an accepted standard of care in the treatment of locally advanced rectal cancer [4].

Significant debate exists regarding the best primary end points for clinical trials testing the addition of a new radiosensitising agent to CRT. Pathological complete response (pCR), the absence of viable tumour cells within the resection specimen, is commonly used but evidence is indeterminate as to whether this translates into improved outcome in terms of overall survival and disease-free survival (DFS; the time from randomisation until local or distant disease recurrence, or death) [5]. Other potential surrogate outcomes include downstaging rate, R0 resection (complete resection with no residual disease at margin) or circumferential resection margin (CRM: the minimum distance between the nearest extent of the tumour and the resection margin). Failure to achieve a negative CRM is associated with a high risk of local recurrence, but it is unclear as to whether this reflects inadequate surgery or aggressive disease [5]. DFS has been found to correlate with overall

Author for correspondence: T.A. Greenhalgh, Department of Oncology, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford OX3 7DQ, UK. Tel: +44-1865-617330.

E-mail address: tessa.greenhalgh@oncology.ox.ac.uk (T.A. Greenhalgh).

http://dx.doi.org/10.1016/j.clon.2015.11.002

survival in a meta-analysis of colon cancer adjuvant trials [6] and at present is considered the most meaningful primary end point in phase III randomised control trials (RCTs) of CRT, albeit with the need to control for adjuvant chemotherapy. DFS is being used as the primary end point in the ARISTOTLE phase III trial in the UK, which is assessing the addition of irinotecan to CRT for rectal cancer. On account of the controversy over the best end points to use in clinical studies, here we will detail the various clinical outcomes reported in neoadjuvant CRT trials.

Chemotherapy

Irinotecan

Pre-clinical data have suggested that the radiosensitising properties of camptothecin derivatives may relate to the inhibition of potentially lethal damage repair. Irinotecan stabilises topoisomerase-I, an intranuclear enzyme that relaxes supercoiled DNA, by introducing a single-strand break through which the intact strand passes prior to religation. Collision between the irinotecan–topoisomerase I complex and the replication fork results in the formation of double-strand breaks, leading to G2 phase cell cycle arrest and cell death [7,8].

Several early phase trials have assessed the addition of irinotecan to standard CRT with fluoropyrimidines for rectal cancer. Table 1 includes results from larger, published phase II trials, in which pCR rates varied from 13.7 to 37%. An abstract by Jung *et al.* [17] details one of two randomised trials of CRT ± irinotecan. With 142 participants, a pCR rate of 17.2% was achieved in the arm receiving 5-fluorouracil/leucovorin (5-FU/LV) CRT versus 24.2% with a combination of S1, irinotecan and radiotherapy ($P = 0.1$). A significantly higher response rate was found in the latter arm when combining those achieving complete and near complete response (57.6% versus 39.1%, $P = 0.035$).

In a RCT of 5-FU with hyperfractionated radiotherapy versus 5-FU, irinotecan and 45 Gy/25 fractions with boost, Mohiuddin and colleagues [11] showed a pCR rate of 26% in both arms with no difference in rates of tumour downstaging. However, there was a higher proportion of radiotherapy delays in the irinotecan arm, 45% versus 22%. Overall, grade 3–4 toxicity was 51% with irinotecan and 42% without the additional drug; gastrointestinal effects were most common in both arms (37% versus 28%) [11]. These rates were higher than those seen in single-arm trials (Table 1) where radiotherapy and chemotherapy dose intensity was largely maintained. Mohiuddin *et al.* [11] reported late toxicity rates of 6%, lower than expected and again gastrointestinal effects predominated.

Five year outcomes have been published by Yoon *et al.* [15] and Mohiuddin *et al.* [19]. The latter study revealed overall survival 61% (95% confidence interval 47–74%) versus 75% (95% confidence interval 61–85%), distant failure 16%/21% and locoregional failure (LRF) 16%/17% rates without and with irinotecan, respectively. By comparison, in a review of 115 patients who had undergone a regime of CRT with irinotecan/S1 in phase I/II trials, the overall pCR rate was similar at 24%, with 5 year overall survival higher at 87%, DFS 79%, distant failure 17% and LRF 2.6% [20]. The multicentre UK-based phase III ARISTOTLE trial, recruiting since 2011, aims to confirm the potential improvement in outcomes seen with the addition of irinotecan to CRT and is currently set to complete recruitment in autumn 2016 [21].

Oxaliplatin

Oxaliplatin acts as a radiosensitiser through a variety of mechanisms, including causing DNA damage through the formation of inter- and intra-strand cross-links, induction of G2/M cell cycle arrest and blockade of DNA repair [22,23].

The addition of oxaliplatin to neoadjuvant CRT regimens showed promise in early phase single-arm trials, with pCR rates from 13% [24] to over 20% in several trials [25–27]. Five large phase III RCTs have gone on to compare various fluoropyrimidine-based neoadjuvant CRT regimens with or without oxaliplatin (Table 2) with pCR rates between 13.3 and 19.5% in the experimental arm compared with 11.3–17.8% without oxaliplatin. CAO/ARO/AIO-04 was the only trial to show a significant difference between the two arms, with pCR rates of 13% in the control arm versus 17% with oxaliplatin ($P = 0.038$). The ACCORD trial found a difference of 13.9% versus 19.2% ($P = 0.09$) but was powered to detect an increase from 11% to 20% with CAPOX. Of note, a higher dose of radiotherapy was given in the arm receiving oxaliplatin, which makes the results difficult to interpret.

A meta-analysis carried out by An *et al.* in 2013 [37], including results from ACCORD, AIO-04, NSABP R-04 and STAR-01 trials, did favour CRT with oxaliplatin (odds ratio = 1.20; 95% confidence interval 1.01–1.42; $P = 0.04$) with an absolute pCR rate difference of 2.5%. However, PETACC-6 was not included in this analysis and with over 1000 participants showed no significant difference in pCR, 11.3% without versus 13.3% with oxaliplatin ($P = 0.31$). Downstaging rates were also similar at 43.5% versus 41.5%, higher than reported in NSAPB R-04 (23.5% versus 17.9%; $P = 0.2$).

In terms of survival outcomes, recently published results from CAO/ARO/AIO-04 [32] showed a significant increase in 3 year DFS in the investigational group of 75.9% versus 71.2% in the control group (hazard ratio 0.79; 95% confidence interval 0.64–0.98; $P = 0.03$). Of note, the former received oxaliplatin with both CRT and adjuvant therapy, with the control group receiving 5-FU alone. Although PETACC-6 also added oxaliplatin to neoadjuvant and adjuvant regimens in experimental arm B, interim 3 year results indicated no significant improvement in DFS, being 73.9% (95% confidence interval 69.5–77.8%) versus 74.5% (95% confidence interval 70.1–78.3%) in arm A, higher than anticipated. Follow-up is ongoing, but these results appear similar to the NSABP R-04 and ACCORD trials, which did not specify adjuvant chemotherapy regimens and reported no significant differences in DFS at 5 and 3 years, respectively.

Although in ACCORD, Dworak TRG score (hazard ratio 0.68; 95% confidence interval 0.59–0.79) was found to be significantly correlated with 3 year DFS on multivariate