Clinical Oncology xxx (2014) 1–11

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Emerging Opportunities for the Combination of Molecularly Targeted Drugs with Radiotherapy

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Received 29 November 2013; received in revised form 29 January 2014; accepted 11 February 2014

Abstract

Recent drug discovery developments in the field of small molecule targeted agents have led to much interest in combining these with radiotherapy. There are good preclinical data to suggest this approach worthy of investigation and in this review we discuss how this has translated into recent clinical trials. The outcome of clinical trials investigating radiotherapy/targeted drug combinations published in the last 5 years is discussed, as are trials in progress. The perceived future opportunities and challenges in the development of this exciting area are considered.

Key words: Molecularly targeted drugs; radiation; radiosensitisers; radiotherapy

Statement of Search Strategies Used and Sources of Information

A pubmed search was used to find all publications ($n = 2008$) reporting clinical studies involving radiotherapy in the last 5 years: radiotherapy[Title] OR radiation[Title] AND (Clinical Trial[ptyp]). These were then manually sorted to identify trials involving the use of small molecule targeted agents in combination with radiotherapy. Agents identified in this search were checked again in pubmed for titles combining their name with the term 'chemo-radiotherapy' and on the website http://clinicaltrials.gov for any unreported phase III trials involving the agent.

Introduction

Radiotherapy is a highly cost-effective and clinically effective treatment. Over 50% of cancer patients receive radiotherapy during their treatment and it is estimated that about 16% of all cures can be attributed entirely to radiotherapy, making it the most effective treatment for cancer after surgery [1]. Improvements in the efficacy of radiotherapy have the potential to translate into increased numbers of people cured of their malignancy. Recent progress in cancer research has enabled the identification and development of agents directed at many novel molecular targets, the combination of which with radiotherapy has the real and exciting potential of substantially improving the therapeutic ratio and tumour control.

Molecularly targeted drugs may be divided into two broad categories; those that target specific antigens found on the tumour cell surface (i.e. monoclonal antibodies) and those that act intracellularly (i.e. small molecule inhibitors). Both groups of drugs seek to interfere with specific key molecular pathways involved in tumour cell growth and progression, although monoclonal antibodies may also be used to deliver additional tumouricidal agents, such as toxins or radioisotopes, directly to the tumour cell.

When used in combination with radiotherapy, molecularly targeted agents aim to increase the effect of the radiation on the tumour or decrease the effects on normal tissues. Substantial preclinical data have accumulated to show that these agents can potentially enhance the tumour response to radiotherapy through a variety of mechanisms,

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0936-6555/$36.00 © 2014 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.
http://dx.doi.org/10.1016/j.clon.2014.02.006

including inhibition of tumour repopulation, improvement of tumour oxygenation, redistribution during the cell cycle and alteration of intrinsic tumour radiosensitivity. This overview will focus on recent clinical developments in the use of small molecule inhibitors to augment the effects of radiotherapy. Agents being tested in the context of clinical trials will be discussed and monoclonal antibodies will not be considered.

Targeting Epidermal Growth Factor Receptor

The vast majority of published clinical trials concern the use of inhibitors of the epidermal growth factor receptor (EGFR). Two agents, erlotinib and gefitinib, have been extensively studied in phase I and II trials (see Table 1). Several mechanisms have been identified in preclinical studies by which local tumour control might be improved when radiation is combined with EGFR inhibitors, including direct kill of cancer stem cells, cellular radiosensitisation through modified signal transduction, inhibition of DNA damage repair, reduced repopulation and improved re-oxygenation during fractionated radiotherapy [33].

Both erlotinib and gefitinib are adenosine triphosphate competitive inhibitors of the intracellular catalytic domain of EGFR tyrosine kinase, inhibiting EGFR autophosphorylation and subsequent downstream signalling [34]. Our search revealed 15 phase I and II trials using gefitinib in combination with radiotherapy in a variety of tumour types, including head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC) and glioma. Often gefitinib was combined with other conventional chemotherapeutic agents appropriate to tumour type, e.g. paclitaxel and fluorouracil (5-FU). In general, the studies found gefitinib/radiotherapy combinations to be well tolerated, although a higher than usual incidence of oral dysesthesias was reported in one study [18] and other side-effects included lymphopenia, rash, mucositis and diarrhoea. Protracted severe stomatitis was reported in another study, felt to be related to the addition of gefitinib [23]. One trial in glioma patients was stopped early due to concerns that intratumoural haemorrhage was related to gefitinib use. However, later analysis suggested that rates were not higher than expected [22].

There have been eight published phase II trials involving the use of gefitinib with radiotherapy. Four reported improved survival results, three did not and one showed variable results between risk groups [20,25–31]. Ma *et al.* [20] found that 19% of patients with NSCLC and brain metastasis had a complete response of the metastasis to the combination of 40 Gy/20 fractions whole brain radiotherapy (WBRT) with 250 mg/day adjuvant gefitinib in a 21 patient trial. Thirteen of 21 patients had a partial response, one patient progressed and three had stable disease. The 81% (95% confidence interval 58–95%) overall response rate exceeded the goal per study design. Overall survival was 13 months (95% confidence interval 8.2–17.8 months) and the investigators also noted a positive effect on quality of life [20]. However, Pesce *et al.* [30], also investigating the role of a gefitinib, but in combination with 30 Gy/10 fractions WBRT in patients with NSCLC with brain metastases, had to cease recruitment to the study after 16 patients as the preset boundary for futility was achieved (less than 10 patients alive at 3 months). These 16 patients had a median overall survival of only 6.3 months (95% confidence interval 2.1–14.6 months) with the most common cause of death being central nervous system progression (7/16 patients). In addition, no improvement in quality of life was seen. There were significant radiotherapy fractionation differences between the studies conducted by Ma *et al.* [20] and Pesce *et al.* [30], which may be important and patients were unselected for EGFR status in both studies.

In the management of locally advanced oesophageal cancer patients, encouraging results were seen when gefitinib (250 mg/day) was combined with 5-FU, cisplatin and radiotherapy (30 Gy, 1.5 Gy twice daily) before and after surgery. Gefitinib was continued as maintenance for up to 2 years. The 3 year Kaplan–Meier estimates (versus historical controls) showed improved overall survival (42% versus 28%, $P = 0.06$) [25].

No phase III trials were identified in which gefitinib was used concurrently in an attempt to enhance radiosensitivity, although a single trial exists where the agent was used after radiotherapy in inoperable stage III NSCLC in which there was reduced survival due to tumour progression [35]. This led to the early closure of a phase II study carried out by Ready *et al.* [28]. Despite this, Ready *et al.* showed promising survival for poor-risk NSCLC patients ($\geq$5% weight loss and/or performance status 2, $n = 21$) receiving sequential chemoradiotherapy with gefitinib with a median progression-free survival (PFS) of 13.4 months (95% confidence interval 6.4–25.2) and a median overall survival of 19.0 months (95% confidence interval: 9.9–28.4) in 21 patients. However, good-risk patients (performance status 0–1 and weight loss <5%, $n = 39$) did not show a similar benefit. The trial did not show differences in outcome dependent on EGFR status, but the encouraging survival of poor-risk patients in this underpowered trial led the authors to recommend further evaluation of this subset in another phase II trial.

Erlotinib is believed to have a broadly similar adverse event rate and efficacy (as monotherapy) when compared with gefitinib [36]. All trials reported acceptable tolerability of erlotinib in combination with radiotherapy with the exception of one, in which 60 Gy in 30 fractions was administered concomitantly with temozolomide and erlotinib in patients with glioblastoma (GBM) [6]. Investigators reported grade 3/4 events, including haematological toxicity and fatigue, with three treatment-related deaths (two patients with refractory bone marrow aplasia, one with sepsis) causing the trial to be terminated early. However, this same combination was successfully used in two other studies at similar doses, also in GBM patients, without any treatment-related deaths or unacceptable toxicity [2,4].

Of the phase II trials identified, six reported encouraging efficacy compared with historical controls and three no improvement. Most trials were conducted in HNSCC and

Please cite this article in press as: Searle EJ, et al., Emerging Opportunities for the Combination of Molecularly Targeted Drugs with Radiotherapy, Clinical Oncology (2014), http://dx.doi.org/10.1016/j.clon.2014.02.006