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Anti-Tumour treatment

Targeted agents in non-small cell lung cancer (NSCLC): Clinical developments and rationale for the combination with thoracic radiotherapy

Pek Keng Koh [a,*], Corinne Faivre-Finn [a,1], Fiona H. Blackhall [b,2], Dirk De Ruysscher [c,3]

[a] Department of Clinical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK
[b] Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK
[c] Department of Radiation Oncology, MAASTRO Clinic, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands

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ABSTRACT

In recent years there has been undoubted progress in the evaluation and development of targeted agents for non-small cell lung cancer (NSCLC). A major contributor has been the discovery of molecular subtypes harbouring a critical oncogenic driver mutation, specifically sensitizing mutations in the epidermal growth factor receptor (EGFR) gene and the EML4-ALK gene translocation. Radiotherapy is a cornerstone of therapy for the curative intent treatment of early stage, localized disease; and for the palliation of symptoms in advanced, metastatic disease. In this molecular targeted era there is limited understanding of how best to combine targeted agents with radiotherapy and in general clinical studies with radiotherapy have lagged behind studies of targeted agents with chemotherapy. Here we summarise the progress made to date and highlight future directions.

Introduction

Improving the outcome in lung cancer is arguably one of the biggest challenges in cancer therapy in the world today with an estimated 1.61 million new cases per year being diagnosed in 2008, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total).[1] The 5-year survival has changed only very little over the last 2 decades, with progress lagging significantly behind other common cancers.[2]

Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC). Radiotherapy (RT) plays a major role in their management resulting in up to 70% of patients suitable for treatment with curative intent with non-resectable disease.[3] A third of NSCLC patients present with early stage disease (stages I and II) and are typically treated with surgery, however medically inoperable patients will be considered for RT. A further third of NSCLC patients present with locally advanced disease (stage III). Most of these individuals have T4 and/or N2/N3 disease and are as such considered to be inoperable and will be treated with chemoradiotherapy delivered either sequentially or concurrently. Concurrent cisplatinum-based chemoradiotherapy is the standard of care in good performance status stage III NSCLC, however many patients are not suitable for this approach because of poor performance status, severe co-morbidities or advanced age.[4] Even with combined chemotherapy and RT, with or without surgery, approximately three out of four of patients with stage III NSCLC will progress locally and/or at distant sites.[3,5] The addition of concurrent chemotherapy to thoracic RT mainly impacts on local control rather than distant control. A meta-analysis based on updated individual patient data demonstrated that although concomitant treatment decreases loco-regional progression (HR = 0.77; $p = 0.01$); its effect is not different from that of sequential treatment on distant progression (HR = 1.04; $p = 0.69$).[6] However local control rates with current RT doses (typically 60–70 Gy in 6–7 weeks) are suboptimal with local progression-free survival rates of about 30%, even with concurrent chemoradiotherapy. Studies have suggested that local recurrence rates when assessed with bronchoscopy and biopsy are probably in the order of 60%.[5] We have learned from the stereotactic RT studies in early stage NSCLC that biological effective doses in excess of 100 Gy are necessary to achieve higher rates of local control.[7] With present RT techniques such doses cannot be

* Corresponding author. Tel.: +44 161 4468273; fax: +44 161 4468111.
E-mail addresses: Pekkoh@nhs.net (P.K. Koh), Corinne.Finn@christie.nhs.uk (C. Faivre-Finn), Fiona.Blackhall@christie.nhs.uk (F.H. Blackhall), dirk.deruysscher@maastro.nl (D. De Ruysscher).
[1] Tel.: +44 161 4468200; fax: +44 161 4468142.
[2] Tel.: +44 161 4468568 fax: +44 161 4463299.
[3] Tel.: +31 88445 5666; fax: +31 88445 5773.

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delivered safely due to risk of normal tissue toxicity. Moreover, a recently reported study, RTOG 0617 has demonstrated no benefit from escalating curative intent doses in advanced NSCLC beyond current standard doses (60 Gy) when combined with concurrent and consolidation chemotherapy, even when modern techniques for RT such as intensity modulated RT (IMRT) was utilised in a significant proportion of cases.[8]

It is therefore plausible that a therapeutic plateau has been reached with conventional RT delivered either alone or in combination with cytotoxic drugs. Yet the 4.5% gain in 5 years survival achieved through increased local tumour control with concurrent compared to sequential chemoradiotherapy reinforces the potential to optimise conventional RT doses with the addition of drug treatment.[6]

Thoracic RT also plays an important role in the treatment of stage IV NSCLC for palliation of symptoms, alone or in combination with chemotherapy. [9,10] Generally lower doses of radiation are delivered in the palliative setting and concurrent chemoradiotherapy is not standard due to the increased risk of acute side effects in patients with a limited life expectancy. A systematic review of 3576 patients in randomised clinical trials reported an improvement in survival of 5% at 1 year and 3% at 2 years using higher doses of palliative chest irradiation (e.g. 36 Gy in 12 fractions) compared to lower doses (e.g. 10–16 Gy in 1–2 fractions) respectively in good performance status patients.[10] These results demonstrate that even in the palliative setting there is scope to improve outcomes by optimising existing therapy.

The scientific rationale to combine RT with targeted (or cytotoxic) agents has been eloquently summarised by Bentzen et al.[11] Five exploitable mechanisms describe the radiobiological basis by which a specific drug may interact with RT to improve a clinical outcome. Briefly, spatial cooperation refers to the use of RT for local disease and systemic therapy for micrometastatic or occult disease. The treatments are not envisaged to interact at the cellular level and therefore not required to be given concurrently. In contrast, the following three mechanisms require the drug to be present at the same time as the irradiation. Cytotoxic enhancement describes the enhancement of cell killing by modulating the induction or repair of cellular DNA damage. Biological cooperation refers to simultaneous targeting of different cell populations in a heterogeneous tumour such as a drug targeting hypoxic (relatively radioresistant cells) while irradiation targets less hypoxic cell populations. Temporal modulation refers to the effect of a drug on biological processes occurring in response to radiation and between fractions (DNA damage repair, cellular repopulation or proliferation, reoxygenation and redistribution). The fifth mechanism is normal tissue protection in which the drug reduces acute and/or late toxicity to enable either an increased RT dose to be delivered or reduce toxicity. In NSCLC treated with curative chemoradiotherapy, pulmonary and oesophageal toxicities are the principal dose limiting side effects with attention also to spinal cord and cardiac doses of RT.

This review aims to summarise reported and ongoing clinical trials in the curative intent and palliative settings combining external beam RT with targeted agents. Because of the scope of the current article and the word count limitation, no background information on each of the classes of targeted agents is given. The reader is referred to several excellent reviews and original reports. Table 1 summarises key studies of targeted agents in combination with thoracic RT including those in abstract form.

Methods

A comprehensive computer literature search was performed to identify publications relating to the use of targeted agents and RT. The databases Pubmed and Science Direct (up to September 2011), using the search terms: "non-small cell lung cancer", "targeted agents", "targeted therapies" and "radiotherapy". The phrase terms "novel agents", "radiation" and "lung cancer" were also used. These were then combined with search terms for the following publication types and study designs: original research reports/articles, reviews, systematic reviews, randomised controlled trials, controlled clinical trials, clinical trials, multicentre studies, comparative studies, and prospective studies.

Conference proceedings of the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO) and the 14th World Conference on Lung Cancer 2011 were also searched for abstracts using the same combination of key words, and for relevant publications. The bibliographies of selected papers were then manually searched for relevant publications.

Epidermal growth factor receptor (EGFR) inhibitors

There is a strong pre-clinical rationale to combine RT with epidermal growth factor receptor (EGFR) inhibitors, as the EGFR pathway is related to cell proliferation and DNA repair and a survival pathway that is upregulated by radiation itself.[12–14] The scientific rationale to combine an EGFR inhibitor with RT is therefore principally to exploit the mechanism of temporal modulation and consequently not restricted to patients with sensitising mutations in the EGFR gene that are known to confer enhanced sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib. However, there is suggestion that tumours with an EGFR mutation, such as in exon 21 may be more sensitive to radiation than their wild-type counterparts.[15,16] Equally, molecular mechanisms that are responsible for treatment resistance to anti-EGFR therapy alone are not necessarily relevant when combined with RT (see Review by Baumann et al.[17]). For instance, in rectal cancer it has been shown that a mutated k-RAS protein confers resistance for EGFR-inhibition, while radiosensitisation may still occur because of DNA repair inhibition that is independent of the k-RAS pathway. In NSCLC, the EGFR TKIs gefitinib and erlotinib as well as the monoclonal antibody cetuximab are licenced or show activity in stage IV disease.[18,19] We will therefore mainly focus on these molecules.

EGFR monoclonal antibodies

Cetuximab: After the demonstration that cetuximab could safely be combined with thoracic RT following induction chemotherapy,[20] two phase II studies in good performance stage III patients were conducted, showing a toxicity profile similar to that of RT alone except for cetuximab-related skin reactions.[21,22] In other studies, cetuximab was combined with concurrent chemoradiotherapy.[23–25] Again, toxicity was similar to that of concurrent chemoradiotherapy alone besides grade 3 skin toxicity in 6–20% of the patients, an expected side effect of cetuximab. Median overall survival rates of between 17 and 25 months have been reported (see Table 1). A large randomised 4 arm Phase III study (2×2 factorial design) RTOG-0617 is ongoing at the time of writing and due to complete accrual in 2014. This study evaluates to role of high-dose vs. standard-dose conformal radiation therapy (60 vs. 74 Gy in 2 Gy per fraction) in the setting of concurrent and consolidation chemotherapy (carboplatin/paclitaxel) with or without cetuximab. [NCT00533949, see Table 2: ongoing trials] The high dose radiation therapy (74 Gy) arms (Arm B and D) of RTOG 0617 were recently closed to accrual (July 2011) as a planned interim analysis showed futility. No patient safety concerns were identified, and there was no indication of a statistical difference in high-grade toxicity between arms. The remaining 2 arms randomising patients to 60 Gy with concurrent chemotherapy with or without cetuximab (Arms A and C) remain open to accrual.[8] Due to the experience with chemotherapy and cetuximab,[26,27] biomarker substudies