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Overview

The Challenges Faced in Developing Novel Drug Radiation Combinations in Non-small Cell Lung Cancer

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Abstract

Lung cancer is the most common cancer diagnosed in the UK. Outcomes for patients with this disease remain poor and new strategies to treat this disease require investigation. One potential option is to combine novel agents with radiotherapy in clinical studies. Here we discuss some of the important issues to consider when combining novel agents with radiotherapy, together with potential solutions as discussed at a recent Clinical Translational Radiotherapy Group (CTRad) workshop.

Key words: DNA damage repair; immunotherapy; NSCLC; radiotherapy; umbrella study

Statement of Search Strategies Used and Sources of Information

In this short overview no formal search of the literature was conducted. Papers and work known to the authors of immediate relevance to this topic have been included.

Introduction

In 2012 there were more than 40 000 new cases of lung cancer in the UK [1]. In the treatment of this disease radiotherapy is a central treatment modality [2]. In spite of significant technical developments in radiotherapy, local recurrence rates after curative intent radiotherapy in the treatment of non-small cell lung cancer (NSCLC) remain high [3]. Radiation dose escalation is one potential avenue of optimisation, but is limited by adjacent normal tissue tolerances [4]. Another strategy to optimise the biological effectiveness of radiotherapy is by co-administration of therapeutic agents that preferentially sensitise malignant cells to radiotherapy. Combining cytotoxic chemotherapy with radiotherapy is such a strategy and has been shown to improve both local control rates and overall survival [5,6]. However, the therapeutic gain achieved by adding cytotoxic chemotherapy to radiotherapy is modest (4.5% gain in overall survival at 5 years with concurrent versus sequential chemotherapy) and is associated with increased toxicity [6]. With increasing understanding of the molecular mechanisms underlying radioresistance and the emergence of systemic agents that can target these mechanisms there is growing interest in considering what additional benefit these agents may add to radiotherapy and how to combine the two modalities in the most effective manner.

This strategy of optimising radiotherapy with systemic therapy is principally aimed at those patients whose disease is localised and potentially curable. However, radiotherapy

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is also used for palliation of local symptoms in patients with advanced or metastatic disease [7]. In this patient group, investigators are starting to evaluate how radiotherapy may be used to optimise the efficacy of systemic therapies such as immune modulating agents. This concept in considered in more detail in another paper in this special issue [8].

Here we consider aspects of tumour biology and radioresistance that can be exploited by novel agents delivered in combination with radiotherapy and the important issues to be considered when combining novel agents with radiotherapy in clinical studies. To illustrate these issues and to present potential solutions, we report on the consensus reached at a National Cancer Research Institute (NCRI) Clinical Translational Radiotherapy Research Working Group (CTRad) workshop, held in Glasgow in February 2016, and the resulting plans to develop two umbrella study platforms to successfully test and implement such novel radiotherapy combinations.

Current Systemic Therapy Combinations with Radiotherapy in the Management of Non-small Cell Lung Cancer

At present, concurrent systemic therapy has no established role in combination with radiotherapy in the curative treatment of stage I or II NSCLC. However, approximately one third of patients when diagnosed with NSCLC have locally advanced, stage IIIA or IIIB disease, for which curative surgical treatment is not an option [9]. Those patients who have a good performance status and acceptable lung function can usually be treated with curative intent radiotherapy, and the addition of chemotherapy has been shown to improve outcomes in this population [10]. Radiotherapy as a single agent may be offered to patients whose fitness or comorbidities preclude the use of chemotherapy either as induction treatment or concurrent with radiotherapy. In the last decade there has been a shift to using platinum chemotherapy concurrently with high dose radiation, based on data showing better outcomes when compared with induction chemotherapy [6]. However, this approach is suitable for less than half of patients with locally advanced NSCLC [11,12].

Concurrent chemoradiotherapy is associated with an improvement in survival [6]. Although some discrepancies in practice exist, the preferred chemotherapy regimen is usually based on a platinum-containing doublet [2]. The optimum radiotherapy dose and fractionation to combine with systemic treatment is less clear. Currently most reported regimens deliver 2 Gy per fraction, 5 days per week, to a total dose of 60–66 Gy.

This issue has been the subject of a number of clinical trials. Most recently the results of the RTOG 0617 study were reported, in which patients were randomised to 60 Gy in 6 weeks versus 74 Gy in 7.5 weeks and, in a 2×2 design, were also randomised to the addition or not of cetuximab to concurrent platinum-based chemotherapy [13]. Patients in the 74 Gy arm had poorer survival than those in the lower dose arm (20.3 months versus 28.7 months). The addition of cetuximab for all comers in this cohort did not improve survival, which has been a disappointing finding, given encouraging previous results from the SCATCH pilot study [14]. The outcomes of this trial have undermined the validity of dose escalation alone, using conventional fractionation, as a method to improve local control or survival in NSCLC [15].

Another approach to improving outcomes for patients with locally advanced NSCLC is to alter radiotherapy fractionation, either by increasing the number of fractions delivered each day, delivering the radiation over a shorter period of time (acceleration) or a combination of the two [4,16]. Conversely, achieving acceleration by increasing the radiation dose per fraction (hypofractionation) in stage III NSCLC has also been investigated and in the SOCCAR phase II randomised trial, 55 Gy in 20 fractions over 4 weeks was evaluated in combination with cisplatin and vinorelbine chemotherapy delivered either concomitantly or sequentially [17]. In this study the median survival was 24.3 months in the concurrent setting compared with 18.4 months in the sequential arm and there has been much interest and progress in combining other modified fractionation regimens with cytotoxic chemotherapy [18,19].

Potential Therapeutic Targets to Enhance Radiotherapy Effectiveness

In describing the revised hallmarks of cancer, Hanahan and Weinberg [20] provide a useful framework within which to consider mechanisms through which to increase the tumoricidal effects of radiation. Many of these approaches have mechanistic potential to enhance radiation-induced lethal damage within the tumour cell and are presented in Table 1 [21–28]. It should be noted that a number of studies examining the combination of novel or targeted agents with radiotherapy in NSCLC are underway [29].

Challenges when Designing Clinical Studies Evaluating Novel Agent/Radiotherapy Combinations

Central to the premise of more targeted therapy is an understanding of the molecular characteristics of each patient's tumour. Molecular subtyping has transformed treatment pathways for the systemic management of advanced NSCLC [30] and molecular subtyping will probably be essential in determining the appropriate systemic therapy agent to combine with radiotherapy for a given patient. Molecular subtyping is currently reliant on tissue blocks rather than cytological sample, but many novel methods that seek to optimise molecular analysis are under development [31]. In general, molecular subtyping requires biopsy samples that are representative of the tumour and of sufficient size to permit analysis. Given the impact that tumour biology is likely to have on novel drug and radiotherapy combinations, it is critical that clinical trials in this area include carefully considered, biologically relevant translational components. One challenge is the high degree of tumour heterogeneity that seems to characterise NSCLC