From novel insights in molecular biology to targeted treatment approaches in head and neck cancer

Kevin J. Harrington *

The Institute of Cancer Research, London, United Kingdom

Squamous-cell carcinoma of the head and neck is the fifth commonest neoplasm worldwide. Over 50% of patients present with stage III/IV disease: so-called locally advanced head and neck cancer (LAHNC). For LAHNC, the treatment paradigm has shifted from mutilating, ablative surgery towards organ-preserving concomitant cisplatin-based chemoradiotherapy [1]. Compared with surgery, chemoradiotherapy delivers equivalent or better locoregional control and disease-free survival with significantly better functional outcomes [1]. Nonetheless, 5-year disease-free and overall survival (30–40%) rates are suboptimal [2]. Strategies to improve outcomes by escalating conventionally delivered radiotherapy and/or cytotoxic chemotherapy are appealing, but they pose unacceptable risks of severe acute and late normal tissue damage and threaten chronic structural, cosmetic and functional deficits that negatively impact quality of life [3].

Recent technical developments in physical targeting of radiation delivery, including intensity-modulated and image-guided therapy, offer a way of safely escalating tumour dose without exceeding normal tissue tolerances. Also, a clearer understanding of the radiation-induced DNA damage response (RIDDR) opens up the possibility of developing tumour-selective biological response modifiers to enhance the effect of radiotherapy/chemoradiotherapy. The potential value of such therapies has been proven by the translation of therapy targeted to the epidermal growth factor receptor (EGFR), cetuximab, from preclinical studies to a positive phase III trial in combination with radiation [4]. In addition, small-molecule tyrosine kinase inhibitors have been tested [5,6].

Recently, biological studies have characterised LAHNC as a disease spectrum, divisible into different prognostic groups on the basis of demographic (tobacco exposure), clinical/radiological (T and N stage) and molecular pathological (human papillomavirus (HPV) status) variables [7]. In addition, we are beginning to understand the molecular landscape of LAHNC more clearly [8]. As a result, we can escape the standard model whereby all patients receive treatment according to a 'one size suits all' philosophy. Instead, we are moving towards treatment individualisation according to prognostic risk group.

Until recently, it was accepted that the standard of care for patients with LAHNC was concomitant cisplatin-based chemoradiotherapy. However, recent data on prognostic subgroups suggest that this is a significant oversimplification: patients with poor prognosis disease may receive suboptimal treatment, while those with good prognosis disease may be overtreated with unnecessary risks of toxicity. Therefore, there has been a realignment towards developing effective, molecularly targeted strategies that offer personalised treatment to individual patients based on prognostic factors. The clearest view of prognosis comes from *post hoc* analysis of patients with oropharyngeal cancers treated in the RTOG-0129 phase III trial [7]. This study defined prognostic groups using specific demographic, clinical/radiological and molecular pathological characteristics: (1) poor-risk disease affected 27% of patients with heavy tobacco use, T4 tumours and HPV/p16^{INK4a}-negative status; (2) low-risk disease occurred in 43% with HPV-positive status and little prior tobacco exposure (or, if >10 pack-year smoking history, by N0–N2a nodal status) and (3) intermediate-risk disease was represented by the 30% with either HPV-positive tumours and >10 pack-year tobacco exposure and N2b/N3 neck disease or HPV-negative tumours and <10 pack-year tobacco exposure and T2/T3 tumours.

A particularly attractive approach to targeted therapy focuses on developing combinations of radiotherapy or chemoradiotherapy with targeted agents that modulate RIDDR to exploit differences between malignant and normal tissues. Mutations in p53 have been reported in many LAHNC and correlate with exposure to tobacco/alcohol. p53-mutant LAHNC show relative resistance to radiation, as evidenced by increased locoregional recurrence rates after radical or adjuvant irradiation [9], and reactivation of p53 has been shown to increase responses to radiation/chemoradiation. In addition, abnormalities in DNA repair signalling involving ataxia-telangiectasia mutated (ATM) and meiotic recombination 11 (MRE11) upstream of p53 are associated with radioresistance.

* Tel.: +44 (0) 207 1535157; fax: +44 (0) 207 8082732.
E-mail address: Kevin.Harrington@icr.ac.uk.
1359-6349/$ - see front matter
http://dx.doi.org/10.1016/j.ejcsup.2013.07.048

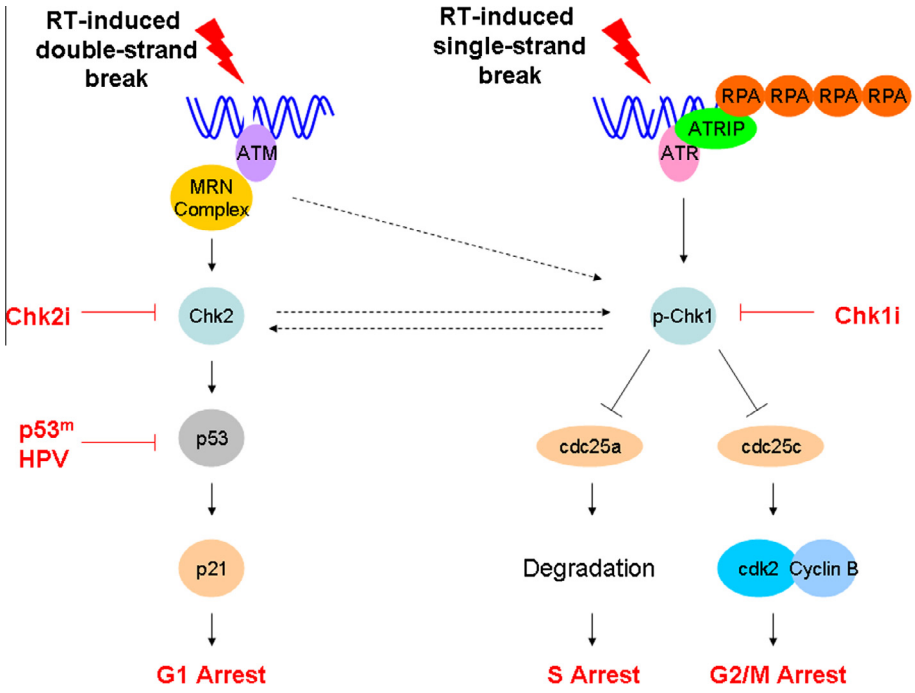

Fig. 1 – Mechanistic basis for targeting S and G2/M checkpoint control in locally advanced head and neck cancer (LAHNC). In human papillomavirus (HPV)-negative, intermediate-/poor-risk disease, p53 mutations render tumour cells reliant on S and G2/M checkpoints to repair radiation-induced DNA damage. HPV-positive, low-risk disease will also rely on this checkpoint (due to viral E6-mediated degradation of p53). Chk1 inhibition, either by relatively specific Chk1 inhibitors or multi-targeted agents (heat shock protein (HSP90) inhibitors), is likely to exert potent radiosensitisation in both prognostic subgroups.

In contrast, HPV-positive LAHNC does not harbour disruptive p53 mutations but, rather, p53 is inactivated by HPV-E6 [10]. In both situations, functional loss of the p53 pathway renders tumour cells reliant on effective G2/M cell cycle checkpoint control (Fig. 1). Also, the importance of repair of single-strand DNA breaks, especially in the context of deficiencies in homologous recombination, is well recognised, and targeting this pathway has been shown to increase the response of head and neck cancer cells to radiation *in vitro* and *in vivo* [11].

There is now significant experience in translational preclinical/clinical studies of small molecules and biological agents in LAHNC. In newly-diagnosed LAHNC, agents that target cell cycle checkpoint kinase 1 (Chk1) and heat shock protein-90 (HSP90) have provided proof-of-principle for the potential radiosensitising effects of modulating DNA damage responses at the G2/M checkpoint. Chk1 is key in cellular responses to DNA damage and replication stress. It is phosphorylated in an ataxia telangiectasia-mutated- and Rad3-related-(ATR-)dependent manner that is required to trigger the G2/M checkpoint and promote homologous recombination. Studies have demonstrated enhancement of radiation-induced cytotoxicity through Chk1 inhibition, but none has been with drugs that have yet entered the clinic [12,13]. HSP90 is a ubiquitously expressed molecular chaperone that exists in a larger complex including HSP70 and co-chaperones (Cdc37, p23, AHA1, Hip and Hop) [14]. HSP90 maintains the conformation of a pool of client proteins that regulate many cell functions. Critically, this includes several signalling molecules and oncogenic proteins that play key roles in cell cycle arrest, DNA damage repair and apoptosis in response to radiotherapy, and a potential advantage of HSP90-targeted therapies lies in their simultaneous combinatorial depletion of many components of the RIDDR. Preclinical HSP90-mediated radiosensitisation has been reported with geldanamycin, its derivatives (17-N-allylamino-17-demethoxygeldanamycin (17-AAG), 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG)), the PU3 purine scaffold derivative BIIB021, and with NVP-AUY922 [15]. In the context of relapsed/metastatic disease, EGFR-targeted therapies have been shown to yield improved outcomes. In addition, a new class of therapies based on replication-competent, oncolytic viruses has entered clinical trials and shown significant promise [16].

In summary, our improved knowledge of the molecular biology of LAHNC has revealed that specific disease subtypes may be amenable to personalised treatment approaches. The challenge for the next decade is to optimise these treatments to improve antitumour effects and to minimise toxic effects in normal tissues.

Acknowledgements

K.J.H. is supported by Grants from Cancer Research UK, Oracle Cancer Trust, Rosetrees Trust, Mouth Cancer Foundation, Get A-Head Charitable Trust, and the Bender Foundation. He has also received research funding from Oncolytics Biotech and Genelux Corporation.

Conflict of interest statement

None declared.

REFERENCES

[1] Lefebvre JL, Ang KK. Larynx preservation consensus panel. Larynx preservation clinical trial design: key issues and recommendations – a consensus panel summary. Int J Radiat Oncol Biol Phys 2009;73:1293–303.

[2] Corvo R. Evidence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol 2007;85:156–70.

[3] Harrington KJ, Nutting CM. Interactions between ionising radiation and drugs in head and neck cancer: how can we maximise the therapeutic index? Curr Opin Investig Drugs 2002;3:807–11.

[4] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.

[5] Harrington KJ, El-Hariry IA, Holford CS, et al. A phase I study to establish the recommended phase II dose of lapatinib in combination with chemoradiation in patients with locally advanced squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27:1100–7.

[6] Harrington K, Berrier A, Robinson M, et al. Randomised phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: rationale for future randomised trials in human papilloma virus-negative disease. Eur J Cancer 2013;49:1609–18.

[7] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.

[8] Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. Science 2011;333:1157–60.

[9] Koch WM, Brennan JA, Zahurak M, et al. P53 mutation and locoregional treatment failure in head and neck squamous cell carcinoma. J Natl Cancer Inst 1996;88:1580–6.

[10] Chung CH, Gillison M. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. Clin Cancer Res 2009;15:6758–62.

[11] Powell C, Mikropoulos C, Kaye SB, et al. Preclinical and clinical evaluation of PARP inhibitors as tumour-specific radiosensitisers. Cancer Treat Rev 2010;36:566–75.

[12] Morgan MA, Parsels LA, Zhao L, et al. Mechanism of radiosensitization by the Chk1/2 inhibitor AZD7762 involves abrogation of the G2 checkpoint and inhibition of homologous recombinational DNA repair. Cancer Res 2010;70:4972–81.

[13] Borst GR, McLaughlin M, Kyula JN, et al. Targeted radiosensitization by the Chk1 inhibitor SAR-020106. Int J Radiat Oncol Biol Phys 2013;85:1110–8.

[14] Pearl LH, Prodromou C, Workman P. The Hsp90 molecular chaperone: an open and shut case for treatment. Biochem J 2008;410:439–53.

[15] Zaidi S, McLaughlin M, Bhide SA, et al. The HSP90 inhibitor NVP-AUY922 radiosensitizes by abrogation of homologous recombination resulting in mitotic entry with unresolved DNA damage. PLoS One 2012;7:e35436.

[16] Donnelly OG, Errington-Mais F, Prestwich R, et al. Recent clinical experience with oncolytic viruses. Curr Pharm Biotechnol 2012;13:1834–41.