Overcoming tumour hypoxia

RAD Magazine, 42, 492, 31

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Background

Cancer occurs as a result of genetic changes and the uncontrolled proliferation of abnormal cells that escape normal homeostatic control mechanisms.1 As tumour growth outstrips blood supply, cells become hypoxic and the decreased oxygen levels stimulate responses to maximise the chance of cell survival. These biological responses to hypoxia promote aggressive features in tumour cells. Also, hypoxic cells are resistant to radiation and some chemotherapeutic drugs. The poor prognosis associated with tumours with low levels of oxygen underpins research into the development of approaches for targeting and overcoming tumour hypoxia.

Hypoxia biology

Oxygen concentration in air is 20.8% (160mmHg), which decreases to 80-100mmHg in arterial blood and 40-60mmHg in normal tissues.2 Median values in tumours range from 28mmHg (breast), 16mmHg (head and neck), 10mmHg (melanoma) to 7mmHg glioblastoma.3 However, these values vary between tumours of the same histological type. In normal tissues, oxygen supply and demand are well balanced. In contrast, the rapid growth of tumour cells consumes oxygen at a rate exceeding supply by the supporting vasculature, leading to regions of hypoxia. Moreover, tumour vessels tend to be immature and prone to collapse, further exacerbating problems with oxygen delivery. As oxygen levels decrease, cells must respond to survive or eventually hypoxia leads to cell death. A key protein involved in this response is hypoxia-inducible factor (HIF)-1α, which is chemically stabilised when oxygen levels fall. This stabilisation leads to the expression of numerous proteins that promote survival, eg angiogenesis to bring in more oxygen. It is this hypoxia response that drives an aggressive cancer phenotype. The association of hypoxia with tumour aggression and a poor prognosis underpinned research attempting to target and overcome hypoxia in cancer therapy. This area of cancer research stems from the work of the radiobiologist Hal Gray who first postulated the existence and importance of hypoxia as a mechanism involved in radiation resistance in the 1950s.

Overcoming hypoxia

Approaches for overcoming hypoxia can be broadly characterised as: increasing oxygen delivery, hypoxia specific radiosensitizers, hypoxia specific cytotoxic drugs, inhibitors of hypoxia induced proteins, and decreasing oxygen consumption. The first approach studied attempted to increase oxygen delivery by placing patients in hyperbaric oxygen chambers during radiotherapy. However, there were logistical issues associated with using hyperbaric oxygen chambers and patients experienced problems in breathing pure oxygen. This led to the development of carbogen breathing (3-5% CO2 plus oxygen = better tolerated) plus nicotinamide (thought to dilate/stabilise blood vessels to increase oxygen delivery). A trial carried out in the Netherlands showed that giving carbogen and nicotinamide with radiotherapy improved the outcome of patients with laryngeal cancer.4 In the UK, the BCON trial showed benefit in bladder cancer,5 and carbogen plus nicotinamide is now included as an option for the treatment of muscle-invasive bladder cancer in the NICE guidelines.6 Other methods explored for improving oxygen delivery include transfusing patients with low haemoglobin levels prior to radiotherapy and using erythropoietin to increase the number of red blood cells and so the oxygen-carrying capacity of blood. Evidence for the benefit of transfusions is mixed and trials of erythropoietin showed no benefit.

The first clinical studies with radiosensitizers involved metronidazole and misonidazole. These compounds are electronic-affinic and mimic the action of oxygen in stabilising the free radicals produced when radiation interacts with tissue, thereby increasing its effectiveness. Several trials were set up during the 1970s, but most failed to find a benefit because they were too small and efficacy was limited by dose-limiting neurotoxicity.7 Despite the failure of most individual trials, meta-analyses showed the benefit of hypoxia modification in radiotherapy with particular benefit in head and neck cancers.8 Efforts to find better tolerated radiosensitizers produced nimorazole. Following the success of a randomised trial led by a Danish group,9 nimorazole is a standard treatment for head and neck cancer in Denmark and Norway. It was not adopted more widely due to problems in obtaining the drug. A fairly recent development was a drug company taking on the production of the drug and obtaining orphan designation by the European Medicines Agency in 2011. Nimorazole is being investigated in the UK in the NIMRAD trial in patients with head and neck cancers undergoing radiotherapy who are unsuitable for concurrent cisplatin or cetuximab.10 NIMRAD also involves the prospective testing of a 26-gene hypoxia signature previously shown to predict benefit from hypoxia modification of radiotherapy in head and neck cancer patients.11 Another trial in Europe is investigating the benefit of adding nimorazole to the current standard of care in head and neck cancer – radiotherapy with concurrent cisplatin.

Another approach for overcoming hypoxia is to use hypoxia specific cytotoxic drugs. Activation of these drugs exploits the reductive environment found in hypoxic cells, ie when oxygen levels are low they are chemically changed from inactive compounds to become or to release cytotoxic species. An example is tirapazamine, which is activated under hypoxia to generate a cytotoxic species. Despite early promise, a phase III trial failed to show any benefit in giving tirapazamine with radiotherapy in patients with head and neck cancer.12 Many factors contributed to the failure, perhaps most critical was a poor radiotherapy compliance.13 Also, no measure of hypoxia was made despite results from phase I/II evaluation showing that a significant benefit from tirapazamine was seen only in patients with the most hypoxic tumours detected using 18F-fluoromisonidazole. Despite early promise, positron emission tomography (PET).14 Evofosfamide is an example of a hypoxia-specific cytotoxic drug that releases a cytotoxic species when reduced in hypoxia. Results are awaited of phase III trials evaluating evofosfamide with doxorubicin in soft tissue sarcoma and with gemcitabine in pancreatic cancer. A phase I trial with chemoradiotherapy in oesophageal cancer is planned in the Netherlands.
Unravelling the biological response to hypoxia identified key proteins as therapeutic targets. An example is EZN-2968 which targets HIF-1α. EZN-2968 is an antisense oligonucleotide, ie it binds to the mRNA transcribed from the gene encoding HIF-1α and prevents the protein being made. A trial in hepatocellular carcinoma is currently recruiting. A downstream target of HIF is carbonic anhydrase IX (CA-IX), which is involved in the regulation of the acidity associated with a hypoxic microenvironment. Both antibody and small molecule-based targeting approaches have been developed. The monoclonal antibody girentuximab was evaluated in a phase III study in renal cell carcinoma. Although the overall trial findings were negative, sub-analyses revealed benefit in patients with high tumour expression of CA-IX. Further clinical studies are using girentuximab to deliver radiotherapy to CA-IX expressing tumour cells. In this radioimmunotherapy approach, girentuximab is tagged with 177Lutetium, a β-emitting radionuclide, which showed promise in renal cell carcinoma in a recent phase II trial.16 Multiple small molecules developed to target CA-IX have shown efficacy in preclinical studies. DTP348 has a dual mechanism whereby activation under hypoxic conditions produces a CA-IX inhibitor and a hypoxic cell radiosensitizer. A Phase I multicentre dose-escalation study of DTP348 is due to open for recruitment in 2016.

Currently, there is also interest in targeting metabolic pathways as an anti-cancer strategy. Metformin targets metabolism and improves tumour oxygenation via a mechanism involving decreasing oxygen consumption. Trials of metformin plus radiotherapy are underway in patients with lung, head and neck, and rectal cancer.

Conclusions

Many approaches for overcoming hypoxia in cancer have been investigated over the past 50 years. Despite a high level of evidence that modification of hypoxia during radiotherapy improves survival in cancer patients, the work had only a modest impact on routine clinical practice. To quote Jens Overgaard1 “hypoxia is adored and ignored” in part due to “a limited commercial interest because most of the solutions are represented by fairly inexpensive drugs and other methods that are not subject to patent”. New approaches for overcoming hypoxia continue to be developed, but recent trials did not exploit research showing the importance of targeting the most hypoxic tumours. A step change in clinical practice requires companion biomarkers of hypoxia (figure 1). There are also numerous approaches for their development of which radiological biomarkers show particular promise.

References


Figure 1

Introduction of approaches for overcoming hypoxia in clinical practice requires the development of biomarkers to identify patients most likely to benefit. Methods for assessing tumour hypoxia include histological analysis of pre-treatment biopsies stained with a marker to identify those with none (A), mild (B), moderate (C) and severe (D) hypoxia. Radiological markers enable pre-treatment whole tumour assessment. Both PET and MRI are of interest and the example shown is contrast enhanced MRI where rapid and high enhancement (E) indicates a well perfused and oxygenated tumour, and slow and low enhancement (F) indicates a poorly perfused and oxygenated tumour.