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Editorial

Hot Topics in Radiobiology

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In the last decade, cancer therapy has been dominated by the huge technical advances in radiotherapy equipment, enabling more accurate targeting of cancers and greater sparing of normal tissue. Currently, advanced treatments, such as intensity-modulated radiotherapy and image-guided external beam and brachytherapy, are commonplace, and the use of charged particles such as protons is being rigorously evaluated. The next decade may well be dominated by advances in applied radiobiology. Six of the seven papers in this special issue outline research that could be used clinically within the medium term to either improve tumour control rates or reduce acute and late radiation toxicity.

The technical advances in equipment used to treat humans has been matched by the development of small animal irradiators very similar to the most sophisticated human machines, including proton therapy. Figure 4 in the paper by Karl Butterworth [1] is striking, as it shows that a murine prostate cancer can be effectively irradiated with sparing of the bladder and rectum. This paper, describing progress in modelling radiotherapy response in mice, is an eye-opener for the non-specialist. Differences and similarities between mice and men are well discussed, including differences in whole-body and individual organ radiosensitivity. Differences in immune response between the two species can lead to difficulty interpreting and correlating immunological data obtained from mice to effects in men. Transplant tumour models such as xenografts have limitations and may be replaced by genetically engineered murine tumour models involving genome editing, which is a potentially very exciting tool to evaluate tumour response to radiotherapy in a defined genomic background similar to their human counterpart. Even accepting all the limitations of murine models carefully listed by Butterworth, mouse models especially, through the use of genome editing, are highly likely to have a greater relevance to human therapy.

One of the most clinically relevant new concepts in cancer biology is the concept of cancer cell senescence (some may call them sleeper cells). Tabasso and colleagues [2] define senescent cells as being in an autonomous state of permanent growth arrest. The role of senescence has recently become more important in cancer therapy, as it has been shown in some tumour type, such as some lung cancers and glioblastomas, that senescence is preferentially induced rather than apoptosis after treatment with radiotherapy or chemotherapy. The development of a senescent state can have multiple, sometimes contradictory, effects. It can have a positive effect preventing premalignant cells progressing to frank malignancy or a negative impact after chemotherapy or radiotherapy, as cytokines released from senescent cells may stimulate angiogenesis and the regrowth of surviving tumour clonogenic cells. There are a number of sensolytic compounds already approved for diseases other than cancer and these could be tested rapidly as safe dosage and side-effects are known. There have been no widely adopted new treatments for glioblastoma since the publication of the European Organization for Research and Treatment of Cancer (EORTC) trial published in 2005 [3] showing the addition of temozolomide to radical radiotherapy gave a small (2.5 months) but clinically meaningful improvement in survival. Senescent cells in glioblastomas after radiotherapy and temozolomide may contribute to the residual mass effect and may aid tumour regrowth. As the mean survival of such patients even with optimal treatment is only 15 months, a phase I/II trial in glioblastoma patients would be top of our list for clinical trials in this emerging and exciting area of cancer medicine.

The review of Jackson and colleagues [4] of small molecule radiosensitisers and hypoxia-activated prodrugs is a welcome update in the long-running saga of *in vitro* animal studies and clinical trials of hypoxic cell sensitising drugs. We were most interested to learn that trials evaluating Nimorazole are still in progress. The authors chart the development of Tirapazamine, which once looked so promising up to the end of clinical studies. Hypoxia activated prodrugs so far

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have had no clinical impact, albeit the lack of associated biomarkers for hypoxic tumour/patient selection masking benefit, so contributing to these studies' perceived failure. But prodrugs leading to DNA repair inhibition look the most promising avenue of investigation, although with a risk of sensitising normal tissues as well as tumours. Short large fraction stereotactic radiotherapy schedules with less prospect of tumour cell re-oxygenation during radiotherapy certainly offer new opportunities to test hypoxic cell sensitisers, but the authors rightly emphasise the importance of identifying hypoxic tumour biomarkers plus those for activation of reductases and stratifying for these factors in any new trials. They also point out that before being evaluated for clinical studies the micro-pharmokinetics of any new agent needs careful testing to check if the agent is actually reaching the hypoxic cells in the tumour.

Minten and Yu [5] discuss the 'two-edged sword' nature of DNA damage repair (DDR). Deficiencies in DNA repair lead to accumulation of mutation and ultimately cancer. DDR in tumour cells also offers a target for anticancer drugs and is one of the reasons why radiotherapy is an effective anticancer treatment. The types of DNA repair, including single- and double-strand breaks plus cross-linkage repair, are well discussed and this paper is highly recommended to trainees. The strength of this paper is the discussion of possible clinical applications of DDR inhibition. Poly ADP-ribose polymerase (PARP) inhibitors are already in use in the clinic and Olaparib has an established place in the treatment of acquired or inherited BRCA mutations together with chemotherapy in ovarian cancer and BRCA-related breast cancer. The role of PARP inhibitors and radiotherapy is just being explored. Apart from PARP inhibitors, most attention has been given to various kinases, but as the authors point out, only 4% of DDR proteins are kinases. Ataxia mutated protein (ATM) seems currently the most potentially therapeutically important, together with its downstream inhibitor checkpoint kinase and DNA-dependant protein kinase, which is a major regular of the non-homologous end-joining DNA repair pathway. The ideal DNA repair inhibitor, when combined with radiotherapy, would sensitise only malignant cells and improve the therapeutic ratio. This illusive compound has not yet been found, but the hunt is ongoing and up to date clinical trials are well described.

The review by Anderson [6] of cytogenetic markers of radiation exposure is excellent and clearly has a wide application is assessing the effects of radiation exposure, such as following the accidents at Chernobyl and Fukushima. We wonder if the evaluation of residual chromosome damage in peripheral lymphocytes could have a wider application to elucidate the potential carcinogenetic effects of repeated radiological examinations, including those having multiple computed tomography scans, such as patients with stage I testicular cancer. Another application would be to assess the possible residual effects of radiation exposure in older oncologists, especially those engaged in brachytherapy who received higher radiation doses than staff at present.

Brothwell *et al.* [7], in an absolutely up to date summary, show how radiogenomics may lead to tailormade treatment based on a combination of treatment, clinical and genetic factors. In particular, radiogenomics can contribute to personalised radiotherapy by identifying sufficient genetic variants associated with a patient's risk of developing radiation toxicity. As the cost of genetic testing is rapidly falling, tests to help clinicians and patients decide on different treatment modalities, such as surgery rather than radiotherapy, are a real immediate possibility. This review discusses in detail results from studies of candidate gene and genome-wide association studies and gives useful methodological advice to avoid the risk of false-positive results, such as by using the Bayesian false-discovery probability calculations. It seems to us that as knowledge accumulates, normal genetic variability will play an increasing role in personalising radiotherapy within the near future.

The influence of the body's own circadian rhythms on normal tissue response to radiotherapy is a new and promising area, whereby scheduling treatment when toxicity is less likely, side-effects can be reduced in a virtually cost-free manner. Harper and Talbot [8] describe very clearly how the body clock functions and the biological factors involved in the circadian cycle. There is already a body of evidence, especially from Francis Levy's group, [8] that toxicity from chemotherapeutic regimens mainly used to treat colorectal cancer can be reduced by altering treatment time, although this has not been adopted in clinical practice, as often this would require nocturnal treatment. The situation may be more straightforward at least for breast radiotherapy, as in some patients, acute and late side-effects of radiation treatment can be increased after morning treatment. In the only genetically based study of effects of timing of radiotherapy to date, pre-noon treatment increased normal tissue toxicity and was associated with normal variants of a number of genes, including PER3, which governs the timing of normal skin cell division. Although the factors influencing circadian variations are likely to be complex in modulating toxicity, the current hypothesis to explain excessive morning side-effects in some patients is centred on the timing of skin cell division. Normally, skin enters the most radiosensitive phase of the cell cycle late in the day to avoid the effects of solar ultraviolet radiation. It is postulated that in those with excessive pre-noon toxicity and variant body clock genes, especially those with a variant PER3 gene, the skin divides earlier in the day and more cells are in the most radiosensitive G2/M phase of the cell cycle at the time of treatment [9]. More work is continuing, but taking into account individual body rhythms may extend the genetic personalisation of radiotherapy as described by Brothwell *et al.* [7] further and whether the patient is a 'lark' or an 'owl' will probably be taken into account by the radiotherapy manager when allocating treatment times in the near future.

Conflicts of interest

The authors declare no conflict of interest.

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