Translational Research—A New Entity?

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The term 'Translational Research' has been increasingly used during the past decade. Julie Denekamp defines the term as 'involved with the detailed assessment of the factors influencing tumour specificity of action in order to achieve the successful implementation of a laboratory concept into a clinical protocol'. Translational research needs laboratory and clinical research units with dedicated staff who can work together. Only the careful planning and performance of clinical trials gathering all the data that may relate to the response of tumour and to that of normal tissues will allow advances in knowledge and lead to improvement in the care of patients with cancer.

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Only in the past decade has 'Translational Research' become a term that is well used in lectures and print. Those who use it rarely give a definition, but not so Professor Julie Denekamp, who defines it as 'involved with the detailed assessment of the factors influencing tumour specificity of action in order to achieve the successful implementation of a laboratory concept into a clinical protocol' (1).

New terms regularly appear and often, on reflection, we find that they describe an activity we have long pursued. Here, with translational research, certainly we have in the past worked hard to find the right conditions necessary to take full advantage of a laboratory advance.

However, although not entirely new, the use of this term does serve a real purpose. It has grown out of our frustration in trying to achieve advances by application of exciting concepts from the laboratory and having so many disappointments. The emphasis upon translational research is important because it highlights the problem area where laboratory and clinical scientists must work in close collaboration in order to gain the benefits for patients with cancer that can come from fundamental work at the laboratory bench.

RESOURCES REQUIRED FOR TRANSLATIONAL RESEARCH IN THE LABORATORY

In the autobiographical proceedings completed prior to the symposium dedicated to Professor Julie Denekamp, Julie has set no fewer than 30 questions that she felt most needed to be asked about any new therapy (1). They are, for example, concerned with understanding the mechanism by which a new therapy works; the likely differences in response between tumour and normal tissues; the short-term and the long-term effects; the magnitude of the benefit likely to be achieved; the margin of safety; the critical scheduling; the relevance of the model; the types of tumour likely to show response and the interactions with other modalities which may be seen.

Julie concentrates upon the creation of staff and resources to carry out studies required in the laboratory, so that the clinical application can be advanced, the premature abandonment of a promising technique avoided and the proof of value of effective methods completed without delay. This would increase the use of animal tumour models (2) and in particular laboratory systems for measuring radiation change in normal tissues—work that has been less frequently funded in recent years.

Julie concluded that, 'we should perhaps not be asking whether translational research groups should be funded, but rather whether a society can continue to afford not to!'

RESOURCES REQUIRED FOR TRANSLATIONAL RESEARCH IN THE CLINIC

We would suggest that equally important in the chain of translational research is the clinical research group that works closely with laboratory colleagues to perform sophisticated phase I and phase II studies (Figs. 1 and 2). Guided by the preliminary laboratory work, the clinical

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Fig. 1. Clinical researchers need to take the advice of those working in the laboratory. Michele Saunders, Stan Dische, Julie Denekamp, Ana Marie Rojas and Mike Joiner talking in the Gray Laboratory.

researchers must perform the definitive studies with human tumours and in human normal tissues. These will determine whether the conditions associated with effect in the animal tumour model can be achieved in the clinic and if the effect can really be demonstrated in the human. They must determine the optimum conditions for employment and observe the acute and late toxic effects together with any combination of effects, particularly when a drug is being combined with radiotherapy. Those working with radiation science must be familiar with the long-term problems and be able to determine potentiation; a challenging task of extreme importance.

A PAST HISTORY TO BE PROUD OF

Radiation therapy and radiobiology has a long history in the field of 'translational research'. In the first half of the 20th century an enormous effort was made to determine the optimal fractionation. At the start there was some laboratory basis to suggest a move from a single treatment to a few treatments. In the 1930s conventional radiotherapy, where 1.8 to 2 Gy was given daily for 5 days of the week for 6 to 7 weeks, became established entirely by clinical experiment and led to a great advance (3). Perhaps it became too well established, so that further advances had to wait to the closing decades of the century before progress could be made.

Fig. 2. Laboratory researchers need feedback from the clinical research group. Stan Dische and Julie Denekamp.

In an era in which cytotoxic agents moved from the demonstration of activity in tumour cell culture models straight to phase I and phase II testing, a more sophisticated approach was employed with hyperbaric oxygen. It should be recalled that Churchill Davidson et al. performed a critical determination of effect in an experiment performed in 8 patients where the tumour was divided in half and where they directly compared the effect of giving 10 Gy in hyperbaric oxygen to that of a similar dose given under normal conditions in air (4). Hugh Thomlinson, then a pathologist, looked at the histological samples and noticed in 7 of 8 examined cases that there was a greater effect in the area treated in hyperbaric oxygen. This remarkable experiment certainly gave proof of principle, but the danger of extrapolation from a single treatment to conventional fractionated radiotherapy was poorly understood at the time. We can also speculate about whether an ethics committee would ever give approval for such a study again.

In testing nitro-imidazoles, extensive in vivo studies of the relationship between dose and the time-scale of serum and tumour concentrations preceded identical studies in humans. Furthermore, in humans, studies of the simultaneous administration of sensitizers comparing serum and tumour concentrations permitted the introduction of the most efficient new drugs. The limited success achieved should not detract from the quality and ingenuity applied to the translational work (5).

The translation of the oxygen effect to clinical benefit began in the 1920s, the principal applications being hyperbaric oxygen, carbogen, the hypoxic cell chemical sensitizers and now ARCON. The product so far has been disappointing, only one practical technique being routinely used—nimorazole for head and neck cancer—and, furthermore, only practised in the country of its development, Denmark. Despite this, the vast effort has taught us many lessons that can now be incorporated into the practise of translational research (6, 7).

Among the important lessons learned from the work with hypoxia must be that many factors influence the success or failure of radiotherapy and modifying just one of them is not likely to advance patient care (8). All known factors must be considered in the design of a clinical experiment in order to improve care. The complexity of human malignant disease and of its response to treatment must be accepted, investigated and exploited; not simply ignored as beyond the effort and energy available to lead to full comprehension.

THE TIME SCALE OF TRANSLATIONAL RESEARCH

The duration of time which elapses between the exciting laboratory innovation and its introduction to the clinic and then from the reporting of the randomized controlled clinical trial to its routine use is often remarkably long. CHART was designed in 1984, taking into consideration laboratory studies that had taken place over the previous decade. Pilot studies began in 1985 and were completed in 1988 (9). It was then agreed that randomized controlled trials should be performed, but it was not until April 1990 that the trials had passed through all the preparatory stages so that case entry could begin. A period of five years was required until adequate numbers were included and this was achieved in April 1995. An initial report was made the following year (10) but the definitive reports concerning the two trials were not published until 1997 and 1998 (11, 12). The implementation into clinical practice in non-small cell lung cancer, is presently still being effected and the approach is still far from being universally accepted even in the United Kingdom where it was developed (13).

Although this time course is depressingly long, in the practice of medicine there is usually a long interval before an innovation, proven to be an advance, becomes accepted and for it to become the standard practice recommended in textbooks. In cardiology, the use of streptokinase immediately after a myocardial infarction is now standard treatment throughout the world, but from the first report of efficacy in a randomized trial it took 30 years for it to become a general recommendation in the textbooks (14).

THE NEED FOR INTERNATIONAL COOPORATION

International efforts should lead to the highest rate of accumulation of cases in randomized control trials and furthermore a result achieved in an international study is more likely to be accepted sooner, and more widely, as best practice if centres in a number of different countries contribute cases to the critical study. As already discussed, nimorazole was shown to be effective as an hypoxic cell sensitizer in the management of head and neck cancer in a multicentre study. The study was, however, performed entirely in Denmark, the only country where it has become a standard in management by radiotherapy (7).

MEASUREMENT AND RECORDING OF MORBIDITY

The scoring of morbidity in randomized controlled clinical trials of radiotherapy is still unsatisfactory. The original EORTC/RTOG scoring system has been widely used, but has been considerably criticized for the admixture of symptoms, signs, investigations and treatments that make up the grades (15). We introduced a dictionary for morbidity in which each individual item making up morbidity was separately observed. It was shown to be more sensitive than existing systems and readily usable in studies conducted in Poland (16). It was also found to be sensitive and practical in the CHART trials. However, in recent years, the LENT-SOMA system has received the widest attention. Introduced in 1995 it separates the different elements but does so in a fairly complex fashion (17). We still wait for this system to be validated for use in the many different sites in the body and there remains a need for an international agreement. Established interests have impeded progress and we wait to see if further meetings can resolve the issues.

DOES TRANSLATIONAL RESEARCH YIELD TOO MANY CONTRADICTORY AND INEXPLICABLE RESULTS?

It is striking that the results of the trial in non-small cell lung cancer, where a highly significant advantage over conventional therapy was demonstrated, are in contrast to the results of the CHART trial in head and neck cancer, where overall there was no significant difference in tumour control and where generally the results have been regarded as failing to advance therapy (10, 11). A significant reduction in the incidence of a number of late side effects of radiotherapy has been acknowledged (18), but this has not influenced the overall assessment of failure. Both studies used an identical scheme of accelerated radiotherapy to a total radiation dose of 54 Gy. In both trials, the control group was treated with conventional radiotherapy employing individual radiation doses of 2 Gy. There are, however, two features that could account for this difference in results.

The first concerns the total doses chosen as conventional radiotherapy. In the head and neck region this was 66 Gy in 33 fractions reflecting acceptable standards within the United Kingdom and also in other countries, such as Denmark. The dose chosen for the small-cell lung cancer patients was 60 Gy, approximately 10% less. This was considered to be compatible with normal tissue tolerance within the large areas of lung and mediastinum that were to be irradiated.

Secondly, in the pilot studies of the CHART trial, the dose prescription was at the minimum within the clinical target area and this was adhered to even when simple opposing portals were used. When the protocols of the randomized trials were drawn up, it was decided that the correct reference dose should be at the intersection point. Reviewing the treatment plans of the cases included in the pilot studies, we found that this effectively reduced the minimum tumour dose achieved within the target volume by an average of 4.5% in the head and neck cases, but only by 1% in lung tumours. The differences can be related to the differing types of field arrangement employed and in

the effect of air transmission upon distribution of dose in the chest.

In the head and neck study, there was a marginal advantage to CHART of local tumour control amounting to approximately 4%, which was, however, not statistically significant. If the radiation dose had been 4% greater and if a gamma value of 2 applies, then the difference might have been 12%, which would certainly have been statistically significant (12). One can conclude that a randomized controlled trial should test the exact regimen employed in the pilot study.

A randomized controlled clinical trial in non-small cell lung cancer performed in Australia did not appear to show any advantage to acceleration and this result seemed to contradict that of the CHART study (19, 20). However the latter study included relatively small numbers and a careful statistical consideration showed that there was no incompatibility (21).

It is therefore apparent that by careful examination of study results differences can be explained and furthermore can yield information and teach us invaluable lessons.

THE TRANSLATION OF OUT-OF-DATE KNOWLEDGE

When a randomized controlled trial yields a positive advantage, it is accepted as evidence-based medicine to guide good practice. Quite properly, there is great pressure to use the technique exactly as it was tested. However, there may be a gap of 15 years between the initiation of the pilot study and the acceptance of the result of the randomized control clinical trial. This may lead to a fossilization of practice based upon out-of-date knowledge.

The problem can again be illustrated by examining the CHART trials. When the regimen was designed, there was little evidence to tell us when cellular repopulation of the tumour actually began (9). We now know there is probably a delay before cellular repopulation commences within the tumour, although there is still considerable uncertainty as to when it does get underway (22). Most authorities feel it is unlikely that a human tumour begins significant repopulation earlier than 3 weeks after initiation of treatment (22–24). In these circumstances an extension of the overall duration from 12 to 21 days is not likely to influence the probability of tumour control.

CHARTWEL was devised with the dual objectives of avoiding the problems of weekend radiotherapy while allowing an elevation of total tumour dose to be reached by extending treatment into a third week (25). Because we have such a complete database for the original CHART study, Soren Bentzen was able to calculate that CHARTWEL to 60 Gy was likely to improve tumour control, although there was uncertainty about the degree of benefit; it could be predicted that tumour control at the three years would increase by between 7 and 14 percentage points above the result of CHART (from 19% to between 26 and 33%) without significantly raising the level of acute and late morbidity (Bentzen, Saunders and Dische, unpublished data).

The best practice of evidence-based medicine, however, would demand that a further randomized trial takes place—CHART versus CHARTWEL. At this time it is unlikely that radiation oncologists would find such a study an exciting one since the expected differences in approach are too small. Case accrual is unlikely to be rapid and the study might take 8 to 9 years to complete. With the interest in the addition of chemotherapy, the way ahead is generally thought to be the combination of accelerated radiotherapy with concurrent chemotherapy.

Fortunately, a multicentre randomized control trial is being carried out in Germany and Eastern Europe where, in small-cell lung cancer, CHARTWEL to 60 Gy is being compared with conventional radiotherapy to 66 Gy. This follows two promising pilot studies of CHARTWEL to 60 Gy performed in Mount Vernon and Dresden (25), (Baumann H, personal communication). A positive result of this randomized trial would allow CHARTWEL to 60 Gy to become recognized as best practice and then a randomized controlled trial of CHARTWEL with or without chemotherapy could go forward.

CONCLUSIONS

Translational research needs laboratory and clinical research units with dedicated staff who can work together. The careful planning and performance of clinical trials in gathering all the data relating to the response of tumour and to that of normal tissues will allow advances in knowledge and improve the care of patients with cancer.

Translational research is never an easy path and there are no certain ways of achieving progress. Even collaboration on an international basis may have its disadvantages, since we must ensure that too much control and too much collaboration does not lead to a stifling of that individual creativity and initiative on which so much depends.

Julie has shown us the way to take translational research forward. In the laboratory, the conditions likely to be employed clinically were carefully reproduced: tumour response and particularly that of normal tissues, early and late, were meticulously observed, measured and analysed. Julie was indeed a 'clinician in the laboratory' and this was no better demonstrated than in the work that she performed with Ana Marie Rojas that led to the introduction of ARCON to the clinic (26, 27). Julie's 30 requirements have left us a great challenge but one that we must strive to live up to.

REFERENCES

1. Denekamp J. Translational research. Autobiographical highlights of a 36-year-long journey in cancer research. Umeå, Sweden, February 2001.

2. Taghian AG, Suit HD. Animal systems for translational research in radiation oncology. Acta Oncol 1999; 38: 829–38.
3. Thames H, Hendry J. Fractionation in radiotherapy. London: Taylor & Francis, 1987.
4. Churchill-Davidson I, Sanger C, Thomlinson RH. High pressure oxygen and radiotherapy. Lancet 1955; 1: 1091–5.
5. Dische S. The clinical science of radiation oncology. Regaud Lecture, Malmo, 1992. Radiother Oncol 1993; 28: 93–107.
6. Dische S, Saunders M. Hypoxic cell radiosensitisation—clinical relevance in. In: Kogelnik H, Sedlmayer F, eds. Progress in radio-oncology VI. Monduzzi Editore Int Proc Division, 1998: 205–21.
7. Overgaard J, Sand Hansen HMO, Bastholt L, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5–85. Radiother Oncol 1998; 46: 135–46.
8. Denekamp J, Dasu A. Inducible repair and the two forms of tumour hypoxia—time for a paradigm shift. Acta Oncol 1999; 38: 903–18.
9. Saunders M, Dische S, Fowler J, et al. Radiotherapy employing three fractions on twelve consecutive days. Acta Oncol 1988; 27: 163–8.
10. Saunders M, Dische S, Barrett A, et al. Randomised multicentre trials of CHART vs conventional radiotherapy in head and neck and non-small-cell lung cancer: an interim report. Br. J. Cancer 1996; 73: 1455–62.
11. Saunders M, Dische S, Barrett A, et al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. Lancet 1997; 350: 161–6.
12. Dische S, Saunders M, Barrett A, et al. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol 1997; 44: 123–36.
13. Macbeth F. An uncharted country. Clin Oncol 1999; 11: 71–2.
14. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. JAMA 1992; 268: 240–8.
15. Mitre Meeting. ESTRO Mitre 2000, 10–11 Dec. Brussels, Belgium. Radiother Oncol 2000; 57 (Suppl 1).
16. Maciejewski B, Zajusz A, Pilecki B, et al. Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. Radiother Oncol 1991; 22: 7–11.
17. Overgaard J, Bartelink H. About tolerance and quality. An important notice to all radiation oncologists. Radiother Oncol 1995; 35: 1–3.
18. Dische S, Saunders MI. The CHART regimen and morbidity. Acta Oncol 1999; 38: 147–52.
19. Ball D, Bishop J, Smith J, et al. A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multicentre trial. Radiother Oncol 1999; 52: 129–36.
20. Baumann M. Accelerated radiation therapy in non-small cell lung cancer. Radiother Oncol 1999; 52: 97–9.
21. Bentzen SSM, Dische S, Parmar MK. Updated data for CHART in NSCLC: a missed opportunity. Letter to editor. Radiother Oncol 2000; 55: 85–7.
22. Withers H, Taylor J, Maciejewski B. The hazard of accelerated tumour clonogen repopulation during radiotherapy. Acta Oncol 1988; 27: 131–46.
23. Bentzen S, Ruifrok A, Thames H. Repair capacity and kinetics for human mucosa and epithelial tumors in the head and neck: clinical data on the effect of changing the time interval between multiple fractions per day in radiotherapy. Radiother Oncol 1996; 38: 89–101.
24. Fowler JF. Biological factors influencing optimum fractionation in radiation therapy. Acta Oncol 2001; 40: 712–7.
25. Saunders MI, Rojas A, Lyn BE, et al. Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated radiotherapy week end less) in non-small cell lung cancer. Br J Cancer 1998; 78: 1323–8.
26. Rojas A, Joiner MC, Denekamp J. Extrapolations from laboratory and preclinical studies for the use of carbogen and nicotinamide in radiotherapy. Radiother Oncol 1992; 24: 123–4.
27. Bussink J, Kaanders JHAM, Van der Kogel AJ. Clinical outcome and tumour microenvironmental effects of accelerated radiotherapy with carbogen and nicotinamide. Acta Oncol 1999; 38: 875–82.