Roger Stupp: What's so ethical about strangling research?

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Patients are losing out because the rules governing research are designed to restrain rather than facilitate. It's got to change, says Roger Stupp, who is frustrated that 10 years after helping set a new standard of care for glioblastoma, patients are still waiting for something better.

Until ten years ago, the average life expectancy for someone diagnosed with the most common brain tumour, glioblastoma, was one year. The route for patients was radiation therapy to hospice. But the discovery in Switzerland of a new therapy combining radiotherapy and chemotherapy changed all that.

The new treatment increased survival rates at two years from 10.9% to 27.2%, and has become the international standard. For people with primary brain tumours – often younger men and women with young families for whom every extra day is precious – the impact has been enormous. Around 5% of cancer diagnoses are primary brain tumours, and they are still usually fatal: but they are no longer seen as hopeless cases.

The story behind the breakthrough is one of luck, people coming together at the right place at the right time, professional commitment, and a young oncologist prepared to make the most of what seemed the most unpromising opportunity.

He was Roger Stupp, today the President of the European Organisation for Research and Treatment of Cancer (EORTC), Professor at the University of Zurich, and Director of both the Department of Oncology and the Zurich Cancer Centre at the University Hospital Zurich. This year Stupp won both ESMO's distinguished Hamilton Fairley Award for lifetime achievements in cancer science and clinical/laboratory research, and the US Society for NeuroOncology's Victor Levin award.

The implications of his discovery continue to

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reverberate. Stupp has presided over the development of molecular characterisation in brain tumours, which helps target the right treatment to the right patient, with all the benefits that can bring for quality of life. He has seen neuro-oncology develop from an unpopular speciality defined by a sense of hopelessness to one which now holds its own in the programme of international cancer conferences.

But today, as one of cancer's leading opinion-formers, he looks back at how the leaps in research and treatment have happened in the past, and wonders if they could ever occur now. Regulation is obstructing advance at every turning, Stupp believes, and he is angry about it. "We have this world of mistrust, no one wanting to take responsibility any more, everyone being defensive."

"The effort required to make progress has increased exponentially," he says. "I know that many clinical trials that need to be done are not done because regulation systems make them too complex and too expensive," he says.

What amazes him is how, less than 20 years ago, so much was achieved in very little time, with almost no money.

Born, bred and medically trained in Switzerland, Stupp arrived at the multidisciplinary oncology centre at the University of Lausanne in 1996. He had just qualified in haematology/oncology after spending three years at the Department of Medicine at the University of Chicago in the United States, where he gained experience in haematological malignancy, head and neck cancer and lung cancer. "But in Lausanne, I was put on what other people didn't want to do, and that included brain tumours."

It wasn't long before the head of the oncology department asked him to look into a new pre-market chemotherapy drug called temozolomide. The hospital had stocks of it, available on a compassionate use basis – they had trialled it for melanoma, and trials had also been planned for brain tumours, but patients had never been recruited.

Early research into the drug in the UK, reported in 1997, had indicated that it brought some benefit to those with brain tumours. "It was simply for me to evaluate. Here I was, I had the drug, I used it and had been lucky enough to

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see a couple of patients respond well to it – and when you've seen that for yourself, that makes a lot of difference. When you see young patients dying within a year or less, you have to try to do something more.

"It was a group of patients that had been neglected. There was nothing to offer them, so they were hardly even sent to medical oncologists. They normally went from the radiation oncologist to hospice care."

When deciding what to do next, his American experience of combining different cancer treatment modalities came into play – it was a practice rarely considered in Switzerland. So he and his colleagues put together a protocol investigating an early and aggressive combination of temozolomide chemotherapy with radiotherapy.

He was criticised. Hadn't he considered the effects of late toxicity? "My answer was, if you get late toxicity, then it's a success. With other treatments you would never see late toxicity because the patient died before effects would show."

He collaborated with colleagues in radiation oncology and neurosurgery in Geneva and Lausanne to ensure he could recruit enough patients for his phase II pilot trial, Schering-Plough provided the drug free, and the whole project was funded from the department's own resources. "Of course, everything was done according to the rules, and we made sure we did the pharmacovigilance, reported serious adverse effects, and we were very careful that patients took the correct doses. But in those days there were no unnecessary checks to be done, and we had the leeway we needed. My team and I did the data management, the research nurse put in the extra time to treat patients, we made the blister packs of the drugs ourselves to ensure that patients got the right doses."

The result of the long hours was something unexpected. Stupp saw from the reaction of radiation oncologists that patient outcomes were changing significantly. Double checking the data for the first time, he became aware of its significance. "It was a very special feeling, no question," he says. A phase III trial, in collaboration with EORTC and NCIC (National Cancer Institute of Canada Clinical Trials Group), recruited 573 patients in 15 months – an indication of the demand for a new treatment. After the results were presented at ASCO in 2004, the treatment became the international standard.

But this original breakthrough led to another, which was equally significant. Looking at the trial data, Stupp wanted to know why some patients benefited from the chemotherapy/radiation combination and some did not. So the laboratory research team, led by Monika Hegi, looked at what might be leading to temozolomide resistance on a molecular level. They discovered that survival was best in those patients who carried an inactivated MGMT gene, which meant that testing tumours for methylation of the gene would allow patients to be selected for this aggressive treatment. For the remainder, who were unlikely to benefit, supportive care could be made the priority.

"I remember when we did the first analysis of this data – it was in my crampy little office about 15% the size of this one" – he waves his arm around his current airy room in the University Hospital Zurich, its large windows opening onto parkland – "so it shows you don't need big offices to do big work. Monika Hegi and I were looking at the computer, and I remember saying, do you know what this means? Coming from the lab side she didn't immediately realise why I was jumping up and down."

The finding had an impact on all glioblastoma patients, not just those who responded, because better molecular understanding not only allowed better targeting, but has raised the prospect of finding new targets.

What is more, the speciality has taken off, as more researchers and oncologists have become interested in brain tumours. Up until the late

1990s, there had been a few small collaborative groups interested in neuro-oncology, and ASCO meetings did not have a track devoted to the central nervous system. Today neuro-oncology conferences attract 1000 people or more.

But it's not all good news. Stupp's description of past triumphs is tinged with regret. "The sad part is that here we are in 2014 almost, and radiotherapy with temozolomide is still the standard of care. I would have loved that this protocol could have been replaced by something better."

Currently the mood is again depressed when it comes to brain tumours. For the past decade, trials into new agents – chemotherapy, anti-angiogenics, EGFR inhibitors – have failed to fulfill early promise. Stupp, true to his America-induced enthusiasm for combination therapies, believes that part of the problem is that all these approaches are being looked at as single agents.

"We have competing companies developing molecules that probably inhibit one pathway in a clinical trial," he says. "But of course, when you look at the complexity of the biology, it's logical there will be escape mechanisms. That doesn't mean that the agent isn't good, or that the target isn't good, but as a sole target it won't work."

"What we need is better predictive pre-clinical models, we need to learn more from early clinical trials before moving on to large trials. For example, using molecular imaging to show that an agent inhibits a target, finding ways to repeat biopsies of brain tissue to see what has been happening, being allowed to do early combinations of therapies. While still paying utmost respect to ethics, we need innovative designs which can tell us much more than we are learning at the moment. This is true of all oncology, not just brain tumours."

A strong belief in translational medicine, a propensity for challenging orthodoxy, and the ability to find reward in virtually any field of activity lie at the heart of Stupp's story, taking him from office clerk at the age of 15 to head of one of cancer's most influential research bodies today.

There was medicine in his family – his uncle was a doctor, his father worked in the pharmaceutical industry – but it held no interest for Stupp when he left school early in the 1970s and qualified as a commercial clerk. He started work for a big Swiss food supplier, stacked shelves and quickly progressed into the company's public relations office. He learned a valuable lesson from his boss, who refused to sign letters that Stupp had composed on his behalf. "You wrote the letter, you sign: you are responsible," the

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boss said. The belief in empowering people with responsibility has stayed with Stupp, and it is a lesson that he passes on to the students and junior doctors he supervises today.

He also edited a youth page in a weekly newspaper and considered a move into journalism. At age 18, despite plenty of job offers, he decided that university would give him more career options later in life, so went back to school to get his qualifications and took a medical degree at Zurich's Medical Faculty. Medicine, he says, simply seemed interesting. And, since he found it hard to learn facts by rote, he discovered he progressed fastest if he completely understood things: "There was no end purpose apart from curiosity, and a refusal to accept that I couldn't do some things just because I didn't have a degree. I need my freedom."

He wanted to go to the US so his mentor in Zurich pulled in contacts and found Stupp a placement in haemo-oncology at the University of Chicago. That was his introduction to cancer: "Up until then I'd been interested in the sexy things like cardiology and gastroenterology. But I thought, 'Okay, you take the opportunities when they come.' And I discovered a new world. Everything was research-driven, everything was protocol-driven, you questioned everything, you read original research not textbooks, the professor's door was always open. This was not at all like germanic Switzerland. I thought haemo-oncology was great – being a doctor paired with research, biology and innovation, interaction with lots of people. I knew it was for me." Every day he started work at 7.30, left at 7.30pm to enjoy the nightlife of Chicago, returned at 11pm and worked until 2am.

He returned to Zurich to finish medical school, went back to Chicago to complete his oncology training, came to the University of Lausanne Medical Centre in 1996, and stayed there for 17 years working in lung and head and neck tumours as well as brain tumours.

"At the beginning I had very low expectations of neuro-oncology. It wasn't popular because it was considered difficult. People like to go into something that is advancing, but this was not the case. It's very difficult when you have nothing to offer to the patient. But I take the challenges as they come and very quickly things

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changed. I found it gratifying because I learned by collaborating with neurologists just how much you have to take care of toxicity, cognitive function and patient factors that perhaps were becoming neglected in the 1990s as we were giving higher and higher doses of therapy. So it opened my mind."

He rose through the ranks, from head of the oncology clinic at Lausanne University Hospital to head of clinical research in oncology in 2001, then on to master of teaching and research at the university's biology and medicine faculty in 2006. In 2008 he became head of the Department of Oncology-Hematology at the hospitals of Vevey and Monthey, and head of neuro-oncology at the Department of Neurosurgery at Lausanne University Hospital.

After 17 years in Lausanne, he needed to energise himself with a new environment, and last August he returned to University Hospital Zurich, where he had received his medical training, to take up the positions of Director of the Department of Oncology, Director of the Zurich Cancer Centre and Professor at the University of Zurich. There's considerably more management for him here, as he tries to build a truly multidisciplinary cancer centre with patients at the heart of structures. Making sure that the young people around him can thrive is a priority: Stupp is keen to build strong teams, and pass on all those lessons about taking responsibility and asking questions that he learned in his medical education.

He also wants junior doctors to have the freedom to inquire that he has had. This is why one of his main priorities, in the midst of his three-year term as President of EORTC, is to speak out against the regulation that he believes is choking innovation and investigation at its very source. He is not just talking about the EU's Clinical Trials Directive – he wants to see an end to the complex mesh of inconsistent rules and protocols that entangle collaboration and progress in Europe.

"I'm not against regulation," he says, "but it has to serve a purpose and currently regulation is just for the sake of regulation." An overwhelming burden of paperwork prevents doctors from spending time on the business that makes them good doctors – interacting with patients, being curious, translating clinical practice into research.

"Apparently in clinical research we are all crooks, we all don't want the best for our patients and we all have conflicts of interest. That is the assumption. Of course I have potential conflicts of interest, but that doesn't mean that my work is influenced. If you think about it, as a doctor I'm making a living out of treating patients – so that's already a potential conflict of interest. So shall we have civil servants as doctors?

"You need people who are responsible, but in this world of mistrust you take away people's responsibility: everything that is not explicitly allowed is forbidden. Stupid. It should be the other way around – you regulate as much as is needed but as little as possible.

"Do you really think that researchers don't want the best for their patients? How do you think it feels when ethics committees tell us that something we are doing is unethical, when we have a protocol which we haven't just discussed in my office, but in a collaborative group according to EORTC protocols involving up to 30 people, over many days? How do outside regulators know better what is ethical? To me, as long as we don't cure this disease, as long as we are treating patients outside clinical trials when there are clinical trials to be run, that is what is unethical. We need to learn and make progress on every patient we treat."

Stupp acknowledges that the subject makes him angry. It's borne as much out of contact with patients as professional pride. Many patients, he says, are prepared to take risks, to further scientific progress for their children's sake, if not for their own. Some patients have a different

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approach, and that also has to be honoured.

He urges academics to get back into control, so that opportunities are not lost and new funding models are found. It is ridiculous, he says, that if he wanted to conduct a randomised controlled trial of a drug already on the market to see whether a lower dose worked as well as the current standard of a high dose, he would suddenly need new infrastructure, expensive trial insurance, stringent pharmacovigilance monitoring – even though patients would be exposed to lower toxicities. What's more, he would have to find ways of getting the drug free, because health insurance companies would no longer reimburse it. "Something is not right," he says.

His other main worry as EORTC President is the fragmentary nature of the EU: every country has its own healthcare system, its own systems of funding, reimbursement and regulation. This affects not only research – the administrative enormity of organising multicentre trials – but also the flow of knowledge in the cancer community. A universal health system is too big a project, he acknowledges, but EU support for the EORTC research structure, which can function effectively in most EU countries, would go a long way.

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"Instead, you currently have all these national groups. There are too many presidents, too many clubs. The endeavour has become so complex that things are only going to move forward if we all pull on the same rope together – molecular biologists, pathologists, imaging, researchers, clinicians, computer technology, statistics, informatics..."

Stupp is restless for progress and the biggest frustration of his career has been the way that laws and people get in the way of new ideas: "There are too many egos, who ask 'What do I get out of it?' when you come to them with a new idea. That's not the question: the question is, what does it bring to the patient, to science?"

Throughout our interview, Stupp returns to the image of the patient sitting in front of him. What can he tell the patient with a brain tumour? What messages of hope? What quality of life? What expectation of cure or control? From the moment he was reluctantly pushed into neuro-oncology nearly 20 years ago, the politics, the research, the pursuit of academic and clinical freedom, have centred on that.

The number of patients with brain tumours may be small compared with other cancers, he says, but that does not make the need to pursue new options for treatment and quality of life, the need to overcome all those unnecessary obstacles, any less urgent.

"We treat patients, not numbers," he says. "Maybe when pharmaceutical companies are looking at the marketing potential for a new drug, the incidence is important. But when you are sitting in front of me, all that matters is you, a patient." ■