**Optimising drug delivery**

**Professor Marc Reymond** is a researcher and surgeon working to constantly improve people's lives. Here, he explains his efforts to enhance treatment for patients with peritoneal cancer and provides a glimpse into how it feels to make a remarkable scientific discovery.

To begin, can you introduce the pressurised intraperitoneal aerosol chemotherapy (PIPAC) research project?

To be effective, anticancer drugs must penetrate tissue efficiently. In patients with tumours confined to the peritoneal cavity, there is established pharmacokinetic and tumour biology-related evidence that intraperitoneal drug administration is advantageous. However, there are practical and theoretical concerns about intraperitoneal chemotherapy, including adequacy of drug distribution throughout the entire peritoneal cavity, limited direct penetration of drugs into tumour or normal tissue, reduction in the delivery of a drug to the tumour by capillary flow (through the systemic circulation) after regional delivery, toxic effects associated with local transport, and inconvenience and cost associated with the specific requirements of regional transfer. In light of these issues, the aim of our clinical research programme is to improve therapy for peritoneal carcinomatosis by optimising drug delivery.

How are you using PIPAC to treat peritoneal carcinomatosis?

The application of cytotoxics via a pressurised aerosol in the abdominal or thoracic cavity is a new method of intraperitoneal chemotherapy. Low-dose PIPAC is applied through minimally invasive, laparoscopic surgery in an operating room equipped with laminar air-flow.

Applying an aerosol in the peritoneal cavity allows the homogeneous distribution of the chemotherapeutic agent within the abdomen. An artificial pressure gradient is generated that overcomes tumoural interstitial fluid pressure, an obstacle in cancer therapy. This results in a higher local drug concentration compared to conventional intraperitoneal or intravenous chemotherapy, which allows dose reduction without loss of efficacy. At the same time, the plasma concentration of the chemotherapeutic agent remains low, so side-effects and organ toxicity are minimal.

Can you provide an insight into the phase II trial PIPAC-OV1 and the results gathered? How have they affected your approach?

Sixty-four female patients with platin-resistant, recurrent ovarian cancer in the third-line (salvage) situation were enrolled between February 2013 and February 2014. Sixty-two per cent of patients had a radiological tumour response. Tumour regression on histology and peritoneal carcinomatosis index improvement were observed in 76 per cent. There were no treatment-related deaths, and the cumulative overall survival rate after one year was 50 per cent.

PIPAC is well tolerated and active in women with recurrent, platinum-resistant ovarian, fallopian or peritoneal cancer; it warrants further investigation in these patients. We are now planning a prospective randomised clinical trial. We have begun a dose-finding study to optimise the therapeutic protocol, and are recruiting for a phase II study with PIPAC in platin-resistant, recurrent gastric cancer in the second-line situation.

What was it like observing the first evidence for the efficacy of intraperitoneal chemotherapy as a pressurised aerosol in human patients?

Although I, as many other scientists, have been trained in self-criticism and cautious data interpretation, it was an emotional experience to read for the first time the anatomopathology report documenting a complete regression of a platin-resistant peritoneal carcinomatosis in a patient. Of course, we had hoped this would happen on the basis of theoretical thinking and preclinical data, but it was difficult to believe.

Though we did not cure the patient and she died two years later, a cure was not the aim. As with many palliative therapies, PIPAC cannot cure the patient, but it can prolong life – and preserve its quality. This is extremely important for the patients; one cannot imagine how important it is to have hope. Patients with peritoneal carcinomatosis need real hope that somewhere, someone has a science-based approach that they can believe in.

Do you have any achievements of which you are particularly proud?

Perhaps I will answer this question in the future, but when I do I will have to retire. My research achievements are in the future, not in the past, and will never be good enough. Innovation is a difficult process that involves significant challenges and difficulties. We are meeting strong resistance from opinion leaders, reviewers and from grant agencies, and in some cases going beyond critical peer review and scientific argument. However, the large number of objective histological responses, the rapidly increasing number of academic centres implementing PIPAC technology, and the growing interest in our clinical research programme compensates for this. Only solid scientific data will provide answers, and we are working hard to provide the medical community with these data as soon as possible.
Aerosol-delivered pressurised chemotherapy

Investigators at the Ruhr-University Bochum are trialling a method of delivering chemotherapy. Having published the results of a phase II study, the technique could soon become clinical practice for ovarian cancer.

Creating effective anticancer treatments is an ongoing challenge in medicine. For treatments to be successful, they must fully penetrate the tissue of interest, reaching all the cancer cells within and at a concentration sufficient to exert therapeutic effect. However, this is not always possible, and chemotherapy often has limited efficacy. Most research into this problem has focused on chemoresistance, with drug distribution being comparatively neglected.

Distribution of drugs may be particularly important for peritoneal cancer that affects the lining of the abdomen. Evidence suggests that administering treatment directly to the peritoneal cavity (intraperitoneal chemotherapy) may be beneficial, increasing exposure and cytotoxicity. For a cancer with poor survival rates, there is a need for methods to complement the conventional treatment options – surgery and systemic chemotherapy. Due to similarities, this method could treat gastric cancer, the second most common cancer worldwide, and ovarian cancer, the most lethal of the pelvic malignancies.

While intraperitoneal chemotherapy has shown a positive impact on survival, there are many concerns about its implementation. One by one, Marc Reymond is addressing these concerns. Professor of Surgery at the Ruhr-University Bochum, Reymond is conducting research to prove and improve its efficacy and safety. By determining how this form of chemotherapy should be delivered to be most effective and least toxic, he intends to encourage its widespread use and improve the quality of life of patients.

A NOVEL DELIVERY TECHNOLOGY

Reymond has developed a new method of intraperitoneal chemotherapy. The method, called pressurised intraperitoneal aerosol chemotherapy (PIPAC), delivers cytotoxic compounds to the abdominal cavity using pressurised aerosol. This approach has several advantages, such as ensuring the uniform distribution of drugs and generating an artificial pressure gradient that counteracts tumoural interstitial fluid pressure – a major obstacle in cancer therapy.

Many peritoneal cancer patients cannot be treated effectively with systemic chemotherapy. PIPAC aims to change this, giving extra time to patients, as well as enhancing general wellbeing. The method is applied via keyhole surgery in a tightly controlled procedure. “In the first step, a normothermic capnoperitoneum is established with a pressure of 12 mmHg,” Reymond explains. “A cytotoxic solution is aerosolised with a micropump into the abdominal cavity, and maintained in this closed environment for 30 minutes under pressure. The aerosol is then removed through a closed suction system.”

SAFE AND EFFECTIVE

The first results of Reymond’s clinical research programme suggested that PIPAC might be associated with fewer side effects and could be more effective than conventional forms of therapy. Based on these data, the Federal Institute for Drugs and Medical Devices in Germany approved two phase II studies in ovarian and gastric cancer. The recently completed PIPAC-OV1 trial used the technique to deliver two cytotoxic drugs, cisplatin and doxorubicin, over three courses to women with recurrent, chemoresistant ovarian cancer.

To evaluate therapeutic effectiveness, the proportion of patients showing a decrease in tumour size was used as the primary endpoint. Secondary endpoints included histological tumour regression grading and quality of life. The results were extremely encouraging: 62 per cent of patients had an objective radiological tumour response, and in 76 per cent, tumour regression was observed by an independent pathologist, with a cumulative overall survival rate after one year of 50 per cent. Classical side-effects of chemotherapy such as kidney or nerve toxicity...
OBJECTIVES

• To take advantage of physical laws to improve the pharmacology of local drug delivery with the goal of enabling significant progress in treating peritoneal cancer – a fatal disease
• To better human health through innovative therapies, such as a new method of intraperitoneal chemotherapy. The method, called pressurised intraperitoneal aerosol chemotherapy (PIPAC), delivers cytotoxic compounds to the abdominal cavity using a pressurised aerosol

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Marcel Reymond attained a Degree in Medicine in 1986, and an Associate Professorship in 1998 from Geneva University. After gaining his license as a general surgeon, he specialised in surgical oncology. Since 2006, he has been Professor of Surgery at the University of Magdeburg, Germany. He has published over 100 peer reviewed articles, is an inventor of numerous patents and has been distinguished with several innovation awards.

and hair loss were not observed. Taken together, it is possible to conclude that PIPAC is both well tolerated and effective in women with recurrent, chemoresistant ovarian cancer with peritoneal spread.

REDUCING TOXICITY WHILE INCREASING EFFICACY

The first application of PIPAC in humans was in November 2011 in three patients with advanced peritoneal cancer. It showed that the novel method can induce regression of chemoresistant tumours using just 10 per cent of the normal systemic dose of chemotherapeutics. Since then, impressive progress has been made: 700 consecutive procedures have been performed in 300 patients.

Building on this, the first regulatory phase II study confirms the advantages of PIPAC, demonstrating a clinical benefit rate of 60 per cent and excellent safety data. Based on these strong results, Reymond’s group recently began a dose-escalation study to optimise PIPAC for ovarian cancer, and is currently recruiting for patients with chemoresistant, recurrent gastric cancer.

PROVIDING HOPE

While PIPAC remains in its infancy, its pharmacological superiority over systemic delivery for treating peritoneal nodes is already clear – supported by in vitro, ex vivo, animal models and clinical data. Able to induce regression of chemoresistant peritoneal cancer, it meets the clinical need for new and better therapies for a fatal cancer.

As a generic drug delivery technology, PIPAC has potential applications for other pathologies. Reymond will now test it in different types of cancer and parts of the body, while using different drugs. Following demonstrations of efficacy in the abdominal cavity, he is developing new intrathoracic applications, paving the way for new treatments for mesothelioma, another rare form of cancer that commonly develops in the lining of the lungs. Indeed, the opportunities are vast, as Reymond details: “Since a therapeutic aerosol can also be distributed within organ cavities, applications including pressurised intravesical aerosol chemotherapy for bladder cancer or intraluminal endosophageal applications for Barrett’s dysplasia are also under investigation”.

It may also be possible to use pressurised aerosols to improve the efficacy of radiotherapy and administer cytolytic viruses to enhance their uptake into tumour tissues – a major limitation of existing intraperitoneal gene therapy. Already in use in five centres and in the process of implementation in 20 hospitals worldwide, including leading cancer research centres, an exciting future lies ahead.

“PIPAC is a tool that is giving biology access to the operating room and represents an attractive opportunity for surgeons to improve the outcome of surgery by controlling its environment,” Reymond concludes.

Breaking down barriers

Reymond has tackled each major obstacle to PIPAC’s implementation

1. ADEQUACY OF DRUG DISTRIBUTION THROUGHOUT THE ENTIRE PERITONEAL CAVITY

If anticancer drugs cannot reach all the cells within a tumour, their effectiveness is compromised. Physical laws support the superior distribution of drugs within the abdominal cavity if they are administered in gaseous form, like during PIPAC.

2. INCREASED DIRECT PENETRATION OF DRUGS

PIPAC directly delivers chemotherapy under pressure, increasing tissue penetration and inducing the regression of peritoneal tumour nodes up to several millimetres. This is a clear advantage over other delivery routes such as hyperthermic intraperitoneal chemotherapy (HIPEC).

3. DECREASE IN THE OUTFLOW OF DRUG FROM THE TUMOUR BY CAPILLARY FLOW

PIPAC reduces blood outflow from the abdomen over the liver and the abdominal wall during the uptake phase. This increases the pharmacokinetic advantage of regional delivery and limits toxicity.

4. REPEATED APPLICATION

PIPAC allows repeated local application of chemotherapy for up to a maximum of nine sessions. At the beginning, therapy intervals are six weeks, in case of objective tumour regression this can be prolonged to three or six months. This is another advantage over HIPEC.

5. TOXIC EFFECTS ASSOCIATED WITH LOCAL DELIVERY

Advanced peritoneal carcinoma patients generally suffer gastrointestinal symptoms that deteriorate until death. Analysis of quality of life data in 91 patients showed that gastrointestinal symptoms remained stable following PIPAC. Global quality of life improved and disease-related symptoms were stabilised for at least 4.5 months in the majority of patients.

6. ADDED TIME, INCONVENIENCE AND COST

Although it is not yet possible to balance the patient benefits of PIPAC against the costs for the healthcare system, it is feasible to say that PIPAC is a minimally invasive procedure requiring a short hospital stay. The costs of chemotherapy are much lower than systemic palliative chemotherapy with biologicals and HIPEC.