Health Policy Advisory Committee on Technology

Technology Brief

Pressurised intraperitoneal aerosol chemotherapy

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HealthPACT

emerging health technology

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Summary of findings

Pressurised intraperitoneal aerosol chemotherapy (PIPAC) is a new method of applying intraperitoneal chemotherapy as an aerosol. Early studies in patients with peritoneal metastases secondary to ovarian or other abdominal cancers have shown some efficacy; however it is difficult to assess the safety and effectiveness of PIPAC without comparative studies. There is only a relatively small pool of patients that this treatment has been used on so far, and even fewer of these have been reported on, as evidenced by the small studies featured in this Brief. As an experimental technique, it has been used in patients who are quite ill and have already failed multiple treatment regimes, but it may not be limited to that group of patients in the future.

HealthPACT assessment

HealthPACT noted that PIPAC may have significant advantages over existing chemotherapy techniques, which are painful and disabling, and associated with long length of stay and a high risk of adverse events. It was also noted that this technology is slowly diffusing into Australian clinical practice. HealthPACT does not support the introduction of this technology into clinical practice at this time, and recommends that PIPAC should only be conducted under the auspices of a clinical trial. Due to the potential benefits for patients, HealthPACT recommends a further review of the evidence on the use of PIPAC in 24 months.

Technology, Company and Licensing

Register ID	**WP223**
Technology name	**Pressurised intraperitoneal aerosol chemotherapy**
Patient indication	**Patients with primary cancers or metastases in the peritoneal cavity**

Description of the technology

This technology is a way of delivering intraperitoneal chemotherapy as an aerosol. It uses a specially designed single-use micro infusion pump alongside standard equipment (high compression infusion line and high compression injector, used for application of intravenous contrast medium) to deliver the drugs as pressurised aerosols into the peritoneal cavity (Figure 1).[1]

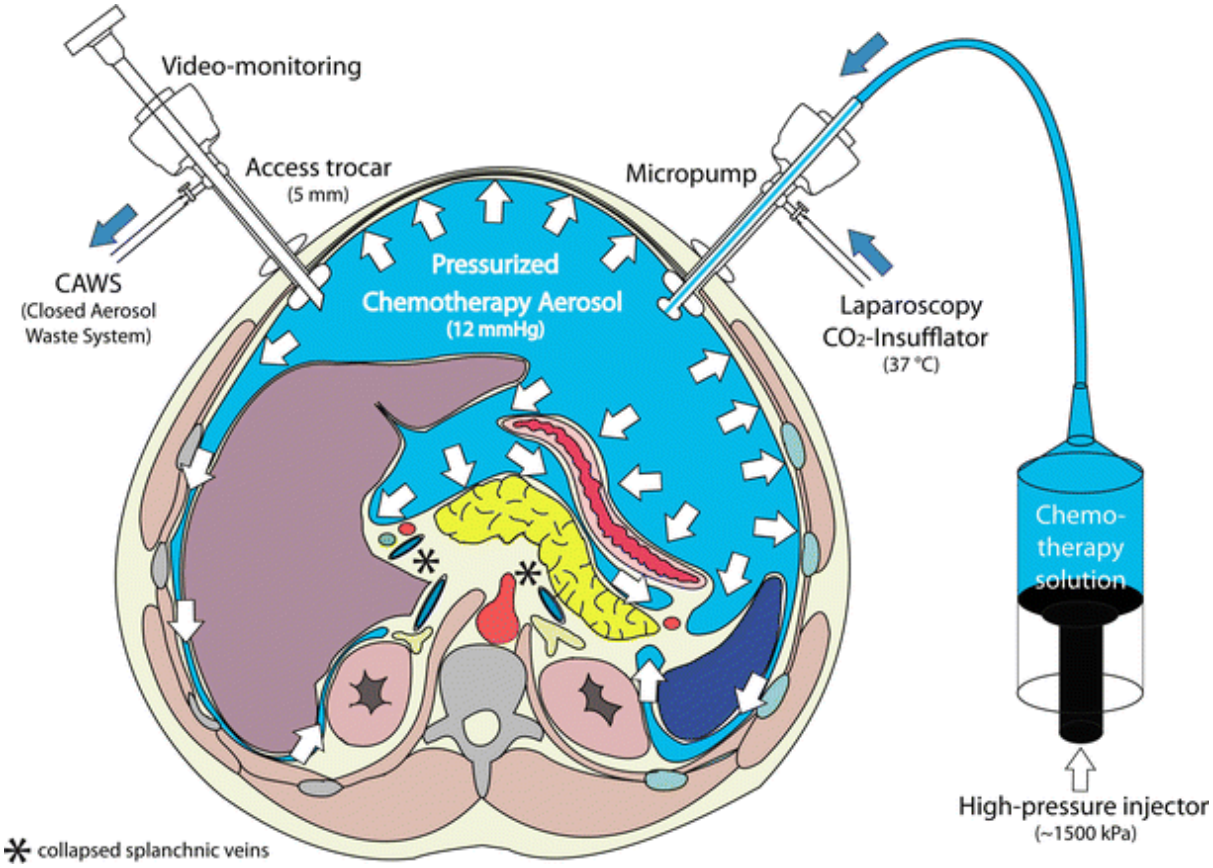

Figure 1: Pictorial representation of PIPAC[2]

The aim of delivering chemotherapy direct to the peritoneal cavity is to increase local availability of the drug whilst decreasing systemic toxicity.[3] However, intraperitoneal chemotherapy, where the cavity is flooded with the drugs, has two major limitations: firstly, poor tumour penetration by the drug, and secondly, incomplete irrigation of the serosal surfaces by the liquid.[4] Hyperthermic intraperitoneal chemotherapy (HIPEC) has been used to try to overcome some of these problems, as cytotoxicity and tumour penetration are

increased at higher temperatures.[5] Even though these treatments exist, survival for ovarian cancer patients (and patients with other peritoneal metastases) is limited; presentation and diagnosis are usually delayed due to the lack of specific symptoms, and disease is often advanced at discovery.

Company or developer

A cancer physician from Germany, Marc Reymond, had the idea to aerosolise chemotherapy in order to improve its distribution in the peritoneum, and he worked with Alexander Hetzel of Reger Medizintechnik to design a micro-pump for this application.[6] Its design was based on an injector used in a car engine, and was used in conjunction with a high-compression infusion line with a commercial high-compression injector for intravenous contrast medium, available in any modern hospital. Professor Reymond and his group, at the Marienhospital, Herne and Ruhr University Bochum, Germany, have been the sole publishers on PIPAC thus far. Reger Medizintechnik have a website dedicated to the use of pressurised aerosol delivery of drugs, called Capnomed (www.capnomed.de).

Reason for assessment

Pressurised intraperitoneal aerosol chemotherapy (PIPAC) is an innovative treatment developed to improve the efficacy of intraperitoneal chemotherapy.

Stage of development in Australia

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

Licensing, reimbursement and other approval

The micro-injector has CE approval as a class 2A medical device; no other approvals were identified.

Australian Therapeutic Goods Administration approval

- ☐ Yes — ARTG number (s)
- ☒ No
- ☐ Not applicable

Technology type	**Procedure**
Technology use	**Therapeutic**

Patient Indication and Setting

The primary indication for this therapy is peritoneal metastases from ovarian, gastric or colorectal cancer. In studies so far, the treatment has been used in patients with recurrent ovarian cancer with peritoneal metastases after intravenous chemotherapy with a platinum compound, or in one case series, a patient each with endstage peritoneal metastases from gastric, appendiceal and ovarian cancer. Currently, intraperitoneal chemotherapy (as first line therapy) is recommended in stage III ovarian cancer patients who have been 'optimally debulked'.[7] PIPAC's place alongside cytoreductive surgery (CRS) or its position in lines of therapy is not entirely clear in the literature; the company states that where CRS with HIPEC is indicated, it should be undertaken. In the larger case study (described later) some of the patients had CRS alongside PIPAC.[8] The company also suggests that PIPAC can be used where CRS and HIPEC are not possible.[9] All patients in the studies so far have already experienced some form of chemotherapy before undergoing PIPAC; indeed, the early studies included terminal patients with no other treatment options and the experiments with PIPAC were granted permission for 'compassionate use' under the German Medical Act.[2 10]

Intraperitoneal chemotherapy and HIPEC are not new. A Cochrane review found that standard intraperitoneal chemotherapy increased survival and progression-free survival in women with advanced epithelial ovarian cancer[3], whilst another systematic review on HIPEC recommended more research before it could be used routinely in women with advanced or recurrent ovarian cancer.[5] A systematic review investigating the quality of life outcomes of patients who had undergone CRS and HIPEC for peritoneal cancers of various origins found a 'demonstrable benefit' for the treatment.[11]

Number of patients

Ovarian cancer was estimated to be the ninth most common incident cancer in females in 2014[12]. The age-standardised incidence of ovarian cancer in 2011 was 10.4 cases per 100,000 women, with 1330 new cases diagnosed in that year. The age-standardised mortality rate was 6.7 per 100,000 in 2012 with 933 deaths from the disease.[13] Five-year relative survival from ovarian cancer was only 43 per cent, compared with 89.6 per cent for breast cancer and 71.9 per cent for cervical cancer.[12] This reflects the late diagnosis of this cancer, due to its non-specific symptoms and lack of screening tools. The rate of cancer recurrence is between 60 and 85 per cent for ovarian cancer, with most recurring in the peritoneum.[14]

In New Zealand, ovarian cancer was the seventh most common incident cancer in females in 2011, with an age-standardised incidence of 8.6 per 100,000. There were 276 new cases registered in that same year. The corresponding age-standardised mortality rate was 5.5 per 100,000. For both registration and mortality, rates were higher for Māori women (11.7 and 9.4 per 100, 000, respectively) than non- Māori (8.2 and 5.2 per 100,000).[15]

In other cancers that metastasise into the peritoneum, colorectal cancer is the most common, however data on the rate of peritoneal metastases in colorectal and other abdominal cancers is limited. One review article estimated that recurrence into the peritoneum after colorectal cancer was 10-35 per cent and up to 50 per cent in gastric cancer patients.[16]

Speciality	**Oncology and radiotherapy**
Technology setting	**Specialist hospital**

Impact

Alternative and/or complementary technology

At this stage, the new technology is used alongside the current technology(ies), in combination with but not replacing them; however as this technique is still in its infancy, there is the possibility that it could replace HIPEC or systemic chemotherapy, or change position in the lines of therapy, should it prove more effective and safer.

Current technology

Current technology is conventional systemic intravenous chemotherapy or intraperitoneal chemotherapy/HIPEC.

Diffusion of technology in Australia

The technology is yet to emerge in Australia; one gynaecological oncologist from Adelaide[1] has undertaken training and is looking to establish the treatment there.

International utilisation

Country	Level of Use		
	Trials underway or completed	Limited use	Widely diffused
Germany	✓		
Denmark	✓		

According to Capnomed, specialists from Germany, Switzerland, the UK, USA, Russian Federation, Argentina, Italy, France, Denmark, Brazil and Austria have been trained and are able to use PIPAC; a senior clinician from the Department of Gynaecological Oncology from the University of Adelaide is also listed as a provider of the treatment.

[1] Contact has been made with this specialist however we are yet to speak to him directly about the technology.

Cost infrastructure and economic consequences

The cost is unclear at the moment as the micro infusion pump is not available for sale; it is a single-use item and therefore would be considered a consumable.

Potential infrastructure requirements for using the technique include the high compression infusion line and high compression injector which the developers suggest are available in any modern hospital as they are used for application of intravenous contrast medium. The operating theatre requires a laminar airflow to ensure safety of the staff and patient from breathing in the aerosolised chemotherapy.

Ethical, cultural, access or religious considerations

No issues separate to the existing issues for treatment with systemic chemotherapy or HIPEC were identified; as a new technology it is likely to only be available in limited settings initially; currently, standard intraperitoneal chemotherapy is recommended to be undertaken only in settings with 'appropriate expertise'.[7]

Evidence and Policy

Safety and effectiveness

All of the evidence for the safety and effectiveness of PIPAC has come from one research group in Germany. Their work was widely shared in 2013 and 2014 as evidenced by the many conference abstracts identified in the search. They have reported on various aspects of the safety and efficacy of PIPAC in the published research, in small case series or single-arm clinical studies, and have also summarised their work in a review article.[14]

The highest quality study was a single-arm clinical study of n=53 women with recurrent, platinum-resistant ovarian, fallopian or primary peritoneal cancer with peritoneal metastases.[8] Women were intended to receive three doses of PIPAC at four to six weekly intervals, however 19 patients received only one or two doses due to disease progression. The drugs delivered were cisplatin at a dose of 7.5mg/m^2 of body surface and doxorubicin at a dose of 1.5mg/m^2 of body surface. Outcomes were objective tumour response measured according to RECIST criteria, histological exam, peritoneal carcinomatosis index (PCI) via laparoscopy, survival, quality of life and adverse events. In the patients who underwent all three doses of PIPAC, a follow up CT scan three months after the final PIPAC cycle was also conducted. Histopathology and radiology were assessed within the study and also by specialists external to the study who were blind to all clinical data. PCI was measured by grading thirteen points within the abdomen on lesion size and distribution; each site was ranked from zero (no visible carcinomatosis) to three (confluent lesions) and the sum of all sites was the PCI. Quality of life was measured using the EORTC QLQ-30 questionnaire at three time points, one day before each PIPAC cycle. Data were presented by intention to treat (ITT) in patients who received at least one dose of PIPAC and per protocol for the

women who completed three doses. There was an objective tumour response in 33/53 (62%) patients in the ITT population, and 16/31 (52%) in the per protocol population. Histological regression was moderate or strong in 33/53 (62%) of the ITT patients and 26/34 (76%) of the patients in the per protocol population. Results are shown in Table 1.

Table 1 Results from treatment with PIPAC in ITT and per protocol populations

Outcome	ITT	Per protocol
Objective tumour response	33/53 (62%)	16/31 (52%)
Regression on histopathological assessment:		
In study assessment	33/53 (62%)	26/34 (76%)
External assessment	38/53 (72%)	30/34 (88%)
PCI improvement	Not reported	26/34 (76%)
1 year survival rate	50%	63%
Mean survival time	331 days (95%CI 291,371)	407 days (95%CI 347, 468)
Mean time to progression	144 days (95%CI 122,168)	174 days (95%CI 150, 199)

PCI: peritoneal carcinomatosis index

Quality of life was not discussed in detail, but the authors reported continuous improvement of global physical health scores during therapy, and increases in physical, cognitive and emotional scores, as well as decreases in fatigue and in the symptom scores for nausea/vomiting, appetite loss, diarrhoea and constipation. They also reported increases in pain and dyspnoea scores during therapy. As the scores were not detailed, the magnitude of these changes is unknown, nor their clinical importance.

In relation to adverse events, no treatment-related deaths were reported, nor any Common Terminology Criteria for Adverse Events (CTCAE) Grade four toxicity. Grade three toxicities in the form of trocar hernia, bowel obstruction, abdominal pain, haematoma, intraoperative bleeding and cystitis with urosepsis were all reported; additionally, there were 32 cases of Grade 2 events (mostly inflammatory, as measured by an increase of C-reactive protein) and 18 Grade 1 events, including ten inflammatory and six cardiac events. All 53 patients experienced Grade 1 abdominal pain.

A case series of n=18 women with peritoneal metastases as a result of ovarian or primary peritoneal cancer was treated with PIPAC or CRS followed by PIPAC.[10] How tumour response was measured in all 18 women is unclear in the report, as much of the discussion

focuses on the eight patients who had more than one cycle of PIPAC, although a response category is given for all participants. Overall, one patient had complete remission, two had partial remission, three had stable disease and 12 had disease progression. The six patients with stable disease or disease remission were all in the group with more than one cycle of PIPAC, hence the author's focus on these women. All but one participant experienced adverse events; five were CTCAE Grade 3 or 4 events. Mean survival time was 442 days, and five women died from disease progression within 132 days of their first cycle of PIPAC. The authors were cautious about their findings recommending trials of PIPAC to investigate it further.

The first case study in humans was undertaken on three end-stage patients with peritoneal metastases from ovarian, gastric and appendiceal cancers. The study achieved complete histological remission in two patients; one of these survived only 109 days after treatment however the other was still alive 567 days post-treatment. The other patient experienced a partial remission and survived 187 days. This patient experienced a bowel perforation during the CRS conducted with PIPAC; other adverse events were CTCAE Grade 2 fever, vomiting and pain in one patient and Grade 1 fatigue in another.

The same research group also published a study of the occupational safety considerations, given that aerosolising the drug may increase the risk of exposure to staff. The study, carried out using simulations and two patients with remote controlled equipment, found minimal risk to staff from the procedure when appropriate precautions were taken.[17]

Economic evaluation

No studies evaluating cost effectiveness or financial implications were identified.

Ongoing research

Two ongoing trials were identified on clinicaltrials.gov. The same research group that has published to date is studying PIPAC in patients with gastric cancer or other peritoneal carcinoma in a single arm, open labels study which is currently recruiting (NCT01854255). A single arm study of the safety of PIPAC for treating peritoneal cancer is currently enrolling by invitation in Denmark (NCT02320448).

Other issues

All of the publications so far have come from the single research group led by the inventor of the technique, Marc Reymond; he also holds the patent for the device.

Other forms of delivery of intraperitoneal chemotherapy are also on the horizon. A review of these methods, published in 2015, reported that the studies so far were only in animals, and investigated drug delivery via microspheres, hydrogel and nanoparticle technologies.[18]

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 3

Total number of Level IV studies: 3

Search criteria to be used (MeSH terms)

Free text:

Pressurized intraperitoneal aerosol chemotherapy

PIPAC

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