Infusing chemotherapy into the liver gives extra months of disease-free life in melanoma patients

September 23 2011

Melanoma of the eye (ocular or uveal melanoma) frequently spreads to the liver and, once this has happened, there is no effective treatment and patients die within an average of two to four months. Only about one in ten patients live for a year. Now, final results from a phase III study have demonstrated that a new treatment significantly extends the time patients can live without the disease progressing.

James Pingpank, associate professor of surgery at the University of Pittsburgh Cancer Institute (Pittsburgh, USA), will tell the 2011 European Multidisciplinary Cancer Congress on Saturday that, by April 2011, the length of time that patients survived without the metastases spreading further in the liver (disease progression) was an average of 8.1 months for those receiving the new treatment compared to 1.6 months in the group of patients that had been randomised to receive the best alternative care.

The new treatment is called percutaneous hepatic perfusion (PHP) and is designed to saturate the liver with high doses of chemotherapy without affecting the rest of the body. The chemotherapy drug melphalan is infused directly into the liver via an intra-arterial catheter over a period of 30 minutes. Blood in the veins leading out of the liver is then captured and filtered through a specially designed, double-balloon catheter to extract the drug before the cleaned blood is returned to the body. This enables the drug to be delivered directly to the liver to target the

melanoma metastases there, but in a minimally invasive manner. The patient is monitored in intensive care before being allowed home. Once the liver has recovered from the toxicity of the treatment, the procedure is repeated every four to eight weeks.

In a phase III, randomised trial that took place in nine US clinics, 93 patients were randomised to receive PHP or best alternative care between February 2006 and July 2009. Best alternative care (BAC) was decided by the patient's treatment team and could involve interleukin 2, ipilimumab, transcatheter arterial chemoembolisation (TACE), systemic chemotherapy or inclusion in a clinical trial.

As the study was not designed to show an overall survival benefit, and most of the patients had no other treatment options available to them, patients were allowed to cross over from the BAC arm of the study to the PHP arm once the benefits of PHP became apparent.

PHP patients had an overall progression-free survival time of 6.1 months versus 1.6 months in the BAC group. Overall survival at one year was 29% on PHP versus 26% on BAC. Due to the fact that 51% of patients crossed over from the BAC arm to the PHP arm, overall survival was not significantly different between the two groups: 11.4 months on PHP versus 9.9 months on BAC. However, those patients who did cross over seemed to do well despite being amongst the sickest, surviving for 9.2 months without the disease progressing in the liver, and 6.5 months without any overall progression of the disease.

Prof Pingpank will say: "This is the first phase III study of PHP in patients with liver-dominant metastatic melanoma and shows that PHP with melphalan significantly improves overall response rates and progression-free survival, providing a new treatment option for the disease. This report includes all data on patients who are more than one year on from inclusion in the trial and we now have all the final response

rates. The only thing that may change over time is the examination of the possible long-term benefits, as all but one of the surviving patients were treated with PHP or crossed over to receive it."

For a disease that currently has few treatment options and no chance of a cure, Prof Pingpank says PHP offers patients extra months of, usually, good quality life. Although the adverse effects of PHP were more severe than BAC, they were short-lived. "Side effects were predominantly neutropenia [low white blood cell count] and thrombocytopenia [low platelet count]. The majority of patients were able to undergo multiple treatments in the PHP arm, as toxicity resolved, whereas the major toxicity in the control arm was liver failure and/or death on treatment from disease progression," he will say.

"This is the first treatment to show a clinical benefit in patients with liver metastases from ocular melanoma. Most patients retain 80% or more of their daily functional status, and return to full performance once therapy is completed. If subsequent recurrence is noted in the liver, retreatment is possible and effective. At this point, it appears that there are groups of patients surviving substantially longer than those control arm of the study, with good quality of liver and preservation of liver function."

PHP potentially could be used for other cancers that have spread to the liver. "We have demonstrated efficacy in a phase II setting for patients with metastatic neuroendocrine tumours [2], so the application of this technology is likely to expand to other tumour types," says Prof Pingpank. "In addition, we have previously demonstrated efficacy of high dose regional melphalan for patients with metastatic colorectal cancer, albeit through a different circuit."

The device that delivers and filters the melphalan has been approved in Europe for use in all malignant liver tumours, while approval is pending in the USA for melanoma only.

Prof Pingpank will conclude: "Certainly, with 50 percent of melanoma patients with metastatic liver disease dying of liver failure, we see this as a frontline therapy for patients with this disease. There is always controversy surrounding the application of regional therapy to patients with metastatic disease, especially when there is a high risk for metastases elsewhere in the body. However, at present, the dearth of options for patients with metastatic melanoma renders this a moot point, and this therapy will be an early choice for patients with liver-only disease."

Former president of ECCO and Director General of the Institut de Cancérologie Gustave Roussy (Paris, France), Professor Alexander Eggermont said: "The maturity of the data presented today better depicts the value as well as the limitations of percutaneous hepatic perfusion. One of the interesting points is that, in these relatively good patients, those that crossed over from the BAC arm of the study have good progression-free survival after a 'late' PHP that is about the same as when PHP is given upfront. In the absence of identified targets for targeted drugs in uveal melanoma, one might consider testing the role of ipilimumab following a PHP."

ESMO spokesman, Professor Ulrich Keilholz, of the Department of Hematology and Medical Oncology and Deputy Director at the Charité Comprehensive Cancer Center, Berlin, Germany, said: "The study by Pingpank is the first phase III trial in uveal melanoma and the first trial to show a benefit of regional treatment for liver metastases in this disease. Given the current lack of targeted drugs in this disease – in contrast to the emerging treatments in cutaneous melanoma – the clinically relevant benefit achieved with melphalan perfusion provides a new reference treatment for patients with hepatic metastases of uveal melanoma."

Provided by ECCO-the European CanCer Organisation