Tailor-made vaccine hailed as milestone in renal-cell cancer

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A new vaccine obtained from the patient's own tumour tissue may offer the first effective adjuvant treatment for renal-cell carcinoma following surgery. The findings of the phase III clinical trial are being hailed as a breakthrough in immunology therapy.

A recent phase III study suggests that a novel autologous tumour-based vaccine could reduce disease recurrences in patients who have had surgery for renal-cell carcinoma (RCC). The results, published in the *Lancet* (2004; 363:594–559) show that the new tumour vaccine lowers the relative risk of metastases and/or relapse in RCC patients by approximately 30% and thereby may prolong their life expectancy. The German study is being hailed as a 'milestone', since it could "serve as a concrete step towards making adjuvant treatment of renal cancer a routine and effective intervention."

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The study's principal investigator, Professor Dieter Jocham of the University of Lübeck Medical School, Germany, is very excited about the results. "The significance of this study is that it's the first ever to demonstrate the benefits of additive therapy for patients with RCC who don't have metastasis, following surgery," he said. "It's also one of the first randomised controlled trials showing benefits for any autologous tumour vaccine."

RCC accounts for 2–3% of all malignancies, with the highest incidence occurring in the sixth decade of life. Of these, 70% are clear-cell tumours; less common cell types include papillary, chromophobe, and Bellini duct (collecting duct) tumours.

The tumour occurs in both sporadic and hereditary forms (the latter accounting for approximately 10% of cases). In sporadic forms, spontaneous mutations have been found on chromosome 3. Smoking and obesity are both risk factors implicated in its development. Other risk factors include exposure to cadmium or asbestos, and long-term intake of diuretics. End-stage renal disease has also been associated with an increased risk of RCC, arising from acquired renal cysts.

Professor Jocham adds pollution as a probable candidate for addition to this list of risk factors. "The incidence of RCC in the Western world is rising by 2–3% each year, and it's likely that environmental pollutants contribute to this increase, although definite causes have yet to be identified," he said.

Treatment options

Removal of all or part of the kidney (nephrectomy) remains the standard treatment for renal cancer. A radical nephrectomy involves perifascial resection of the kidney, perirenal fat, regional lymph nodes and ipsilateral adrenal gland. Lymph node dissection may not be therapeutic, but provides prognostic information, since virtually all patients with nodal involvement subsequently relapse with distant metastases, despite lymphadenectomy.

Nephron-sparing surgery is indicated in clinical situations where a radical nephrectomy would result in patients requiring dialysis. Nephron-sparing surgery is now becoming more widely

used in patients with small accessible tumours with a normal contralateral kidney function. "There's an increasing trend for patients with unifocal RCC tumours less than 4 cm in diameter to be considered candidates for partial nephrectomy, depending on the location of the tumour," said Professor Jocham. "Tumours on the outer surface of the kidney are considered more suitable than those in a central location."

So far, however, no effective adjuvant treatments following surgery have been established for this disease. In studies, various adjuvant protocols – including radiotherapy, interferon alpha, interleukin-2, and medroxyprogesterone acetate – have failed to show promise. "There have been around ten such randomised studies published in the past 20 years, and none could demonstrate a benefit for the patient – defined as improved progression-free survival and/or overall survival," said Professor Jocham, adding, however, that some drugs have been shown to be effective in patients with metastatic disease.

Observation remains the standard care following nephrectomy, with patients being offered abdominal CT scans four to six months after surgery to serve as a base-line. The lack of adjuvant treatment to reduce the likelihood of suffering relapse can leave many RCC patients feeling vulnerable. The relative five-year survival of patients with RCC for all tumour stages is 62%. After radical nephrectomy, 20–30% of patients with localised tumours relapse, with lung metastasis representing the most common site of distant recurrence. Most relapses occur within three years, and the two-year and five-year survival rates of patients with metastatic RCC are less than 20% and 5%, respectively.

Against such limited options, it is understandable that the new adjuvant approach, administering a non-toxic autologous tumour-derived vaccine, is causing considerable excitement.

TAILOR-MADE VACCINE

There are three main categories of cancer vaccine. First there are non-specific immunostimulants such as BCG, interleukin-2, and interferon alpha, which boost levels of activity in the immune system to reverse immunosuppression induced by the tumour. Then there are specific target vaccines that exploit the fact that tumour cells often express different antigens from normal cells, enabling the body to identify as foreign many antigens that occur particularly in malignant tumours.

The trouble is that antigens found in RCC tumours tend to vary from one individual to another, and no specific antigens have yet been defined that are found in all tumours. LipoNova, a biotechnology company based in Hannover, Germany, has therefore developed a 'tailor-made' approach, where vaccine is extracted from each patient's specific tumour material. The autologous vaccine has the advantage that tumour antigens are matched precisely to the patient, with inactivated whole cancer cells containing the entire spectrum of tumour antigens.

"The basic idea behind the vaccine was that each patient's tumour material differs slightly, and therefore the autologous vaccine made from the patient's own tumour tissue might be effectively administered to the person it was derived from, helping the individual immune system fight the disease," explained Jutta Ulbrich, Head of Communications, at LipoNova.

The procedure is as follows. First, the surgeon harvests a 10-g specimen from the peripheral zone of the tumour and places it in a tissue culture medium to be transported to LipoNova's laboratory in Hannover. Here, vaccine production includes in vitro incubation with interferon alpha to increase the antigenicity of the cells, and the addition of tocopherol acetate to protect inner and outer cell membranes during the incubation process. The cancer cells are killed by a devitalisation process involving repeated rapid freezing at -82°C and thawing, without a cryoprotector. Finally, washing procedures remove the interferon alpha, and the result is a pure autologous cell lysate vaccine, with no additional cytokines or bacterial or viral adjuvants present in the injected material. From start to finish, vaccine production takes between four and six weeks.

Professor Jocham and colleagues recruited 558 patients, aged between 18 and 70, who had been diagnosed with a renal tumour and were scheduled for nephrectomy. They were drawn from 55 medical centres throughout Germany, between January 1997 and September 1998. Before surgery, all patients were randomised to receive autologous renal tumour cell vaccine or no additional treatment (the control group). Patients, surgeons and other hospital staff were only told the outcome of randomisation after the surgical procedures had been completed. Ultimately, only 379 patients fulfilled the postoperative inclusion criteria for the study, which was a histologically proven RCC of stage pT2-3b pNO-3 MO.

Administration of the intradermal vaccine usually starts four weeks after surgery. Patients are given six intradermal applications of the vaccine into their upper arms at four-week intervals. They are then evaluated every six months for at least 4.5 years. The primary endpoint of the study was to

reduce the risk of tumour progression, defined by local recurrence or distant metastasis, confirmed by physical examination and/or imaging, or death. Measures of secondary outcomes included the effect of the vaccine on quality of life (to be reported separately) the success of the vaccine production process (total number of tumour cells) and the rate of adverse events.

Effects and side-effects

In the *Lancet* paper, Professor Jocham and co-workers report that the autologous renal tumour cell vaccine improved progression-free survival at five years from 67.8% in the control group (no adjuvant treatment) to 77.4% in the vaccine group. And with time, the benefits for treated patients became even more evident. At 70 months, the figures were 59.3% for the control group, compared with 72% in the vaccine group.

The final results reveal especially prominent differences for patients who are at increased risk of relapse due to their advanced tumour stage (large tumour size, high tumour grade or high Störkel scores). Relapse or metastases were detected over five years in only 32.5% of patients treated with the tumour vaccine, compared to 50.3% in the control group. The investigators add that it is noteworthy that only 12 vaccine-related adverse events were recorded in the study, and these were mild to moderate in severity. They conclude: "According to our results, application of an autologous renal tumour cell vaccine can be considered in patients undergoing radical nephrectomy due to organ-confined renal-cell carcinoma of more than 2.5 cm in diameter."

Since randomisation occurred before surgery, many patients had subsequently to be excluded from the study when histological and postoperative staging results showed that they did not fulfil the inclusion criteria. One criticism levelled at the study is that losing such a large number of patients (32%) after randomisation could lead to an imbalance in the two arms. "The prognostic features tabulated by Jocham and colleagues show that the number of T3 [stage 3 – 1993 TNM classification] subjects are about equal in the two groups, with most of the imbalance in the T2 subset. Although intuitively reassuring for the validity of T3 subset analyses, this finding does not fully compensate for the post randomisation losses," write Mayer Fishman and Scott Antonia from the H Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, in an accompanying Commentary (p 583).

There are also concerns about the choice of progression-free survival as the primary end point, because other adjuvant approaches that have also shown an effect on progression-free survival have been rejected for failing to show an effect on overall survival. The authors say that they chose progression-free survival "because even with surgery for metastatic disease and modern immunotherapy …survival for most patients is between 12 and 18 months, and fewer than 5% survive longer than five years."

They add that since many patients with metastatic RCC enter clinical trials with different combinations of therapeutic approaches, this could vary the effect of the vaccine on individual outcomes, which could complicate the results.

Fishman and Antonia also comment that, since about a third of renal cancers occur after the age of 70 years, using over 70 as the patient age group might have been more appropriate. Professor Jocham agrees that this would be more representative of patients with RCC, but adds that they only recruited patients younger than 70 in accordance with the Helsinki rules of good clinical practice that applied at the time. "These rules have since changed for oncology, and in any future trials we would plan to include older patients," he said.

Despite their reservations, Fishman and Antonia hail the study as an 'immunological breakthrough', and conclude that "the carefully collected data are part of a broadening base of clinical observations of the potential to affect the biology of a solid tumour with non-toxic readministration of autologous tumour-derived material."

While we're waiting...

LipoNova submitted its Marketing Authorisation Application for the vaccine to the European Medicines Agency (EMEA) in December 2003. They hope to obtain the authorisation in 2005, after which they plan to make the vaccine widely available to all patients who would benefit from it.

"We are currently in the difficult situation where, on the one hand we have an obligation to inform patients about the results of the trial, but on the other insurance companies will only reimburse the costs of the treatment after the drug has been officially authorised," said Professor Jocham.

As the autologous vaccine is tailored to the patient's own tumour, it can only be obtained using samples of the patient's tumour tissue, which could be a problem if tissue removed at surgery is destroyed in line with common practice. LipoNova has therefore set up a tissue bank where RCC tumour tissue, removed at surgery, can be stored at no cost to the patient. This ensures that patients operated before the vaccine has been licensed will still have the possibility of being treated at a later date.