Adjuvant Autologous Tumour Cell-Lysate Vaccine versus No Adjuvant Treatment in Patients with M0 Renal Cell Carcinoma after Radical Nephrectomy: 3-Year Interim Analysis of a German Multicentre Phase-III Trial

(renal cell carcinoma / radical nephrectomy / immunotherapy / vaccine / adjuvant therapy)

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Abstract. Even M0 RCC is associated with tumour progression in approximately 30% of all patients after radical nephrectomy. Nevertheless, no effective adjuvant treatment after radical nephrectomy has been established. In a multicentre phase-III trial we investigated the impact of an adjuvant autologous tumour cell-lysate vaccination on the progression-free survival of patients with M0 RCC after radical nephrectomy.

Between January 1997 and August 1998 a total of 558 patients with a renal tumour were enrolled at 55 different centres (study group) in Germany. Prior to radical nephrectomy all patients were centrally randomized (Quintiles Germany) to either receive an adjuvant autologous tumour cell-lysate vaccine (6 applications at 4-week intervals after radical nephrectomy) or to receive no adjuvant treatment (control group) after radical nephrectomy. All patients were evaluated following standardized diagnostic investigations at 6-month intervals. Following the inclusion criteria (RCC stages pT2-3bpN0-3M0, TNM-classification, UICC 1993), 365 patients were evaluable for the 3-year progression-free survival analysis. There were 240 patients with stage pT2pN0M0 (104 in the vaccine group and 136 patients in the control group) and 89 patients with stage pT3pN0M0 (46 in the vaccine group and 43 patients in the control group). The remaining 36 patients had positive lymph nodes. The trial was performed according to ICH-GCP guidelines.

The 3-year progression-free survival rate for all tumour stages was 84.7% in the vaccine group and 80.9% in the control group. Patients with RCC stage pT3pN0-3M0 in the vaccine group demonstrated an advantage (74.4% in the vaccine group vs 65.9% in the control group). For RCC stage pT2pN0-3M0 the 3-year progression-free survival rate in the vaccine group was 89.7.4% compared to 85.7% in the control group. Follow-up of all patients enrolled in this trial is ongoing.

This is the first randomized trial indicating a benefit from an adjuvant vaccination in patients with M0 RCC after radical nephrectomy. The advantage in terms of progression-free survival was more pronounced in patients with T3-tumours. However, it must be emphasized that the results of the final study report (2003) must be awaited before definite recommendations can be made.

Two percent of all malignant tumours in adults develop in the kidney (Figlin, 1999). In 85% of these patients, the tumour originates from cells of the proximal tubules and is known as renal cell carcinoma (RCC) (Figlin, 1999). RCC predominantly occurs in the 6th and 7th decade of life with a male to female ratio of 1.5 to 1 (Motzer et al., 1996; Fischer et al., 1997; SEER 2002).

Tumours are staged using the TNM or Robson classification (Robson et al., 1969; Wittekind and Wagner, 1997). The tumour stage is still the best prognostic indicator for the risk of tumour progression and patient survival (Motzer and Russo, 2000; Tsui et al., 2000). According to recent SEER data RCC is localized in 49%, regional in 22%, distant in 22% of patients with corresponding 5-year survival rates of 89%, 61% and 9%, respectively [SEER 2002]. Various authors reported 5-year survival rates after radical nephrectomy between 57% and 92% for T2-tumours and 35% to 77% for T3-tumours (Dal Bianco et al., 1988; Störkel et al., 1989; Giuliani et al., 1990; Hermanek and Schrott, 1990; Dinney et al., 1992). Patients with metastatic RCC usually have a life expectancy of less than 2 years (Motzer et al., 1996; Figlin 1999; Motzer and Russo, 2000).

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Abbreviation: IFN-α – interferon α, IL-2 – interleukin 2, RCC – renal cell carcinoma.

Standard therapy of organ-confined RCC is radical nephrectomy or partial nephrectomy in case of smaller tumours. However, one of three patients treated for organ-confined RCC will have local recurrence or systemic progression with metastatic disease (Rabinovitch et al., 1994; Sandock et al., 1995; Levy et al., 1998; Figlin, 1999). Attempts to improve survival through the use of adjuvant therapy strategies (hormones, radiotherapy, chemotherapy, immunotherapy, and others) have failed to show any treatment advantage and today there is no consensus on this topic (Finney, 1973; Boon et al., 1994; Migliari et al., 1995; Rammensee, 1995; Yagoda et al., 1995; Makarewicz et al., 1998; Basting et al., 1999; Figlin, 1999; Motzer and Russo, 2000).

In a prospective randomized multicentre phase-III trial we compared radical nephrectomy plus adjuvant autologous tumour cell-lysate vaccine versus radical nephrectomy without adjuvant therapy in patients with RCC. A 3-year interim analysis of this trial is presented herein.

Material and Methods

Patients

Between January 1997 and September 1998 a total of 558 patients with a renal tumour scheduled for operative therapy participated in a prospective randomized multicentre phase-III trial. The protocol was approved by the ethics committee of the University of Lübeck Medical School as well as local ethics committees of the participating clinics. Voluntary, written informed consent was obtained from all patients. Prior to radical nephrectomy all patients were centrally randomized (Quintiles, Germany) to either receive an adjuvant autologous tumour cell-lysate vaccine (6 applications at 4-week intervals after radical nephrectomy) or to receive no adjuvant treatment (control group) after radical nephrectomy. Postoperatively, all patients with histologically proven RCC stage pT2-3bpN0-3M0 (TNM classification, UICC 1993) were definitely included. Clinical parameters such as age, sex, tumour localization and size, T-stages, N-stages, grading, and Störkel-score were also documented (Störkel et al., 1989). The trial was performed according to ICH-GCP guidelines with 199 patients in the control group and 166 patients in the vaccine group. There were 64% men and 36% women with a median age of 59 years. Median tumour size was 6 cm in both groups. RCC stages pT2pN0-3M0, pT3pN0-3M0 and pT2-3bN0 were present in 70%, 30% and 90%, respectively.

Inclusion criteria

Age 18–70 years, ECOG status 0–2, primary RCC stage pT2-3bpN0-3M0 treated by radical nephrectomy, written informed consent. No serious chronic or acute illness such as pulmonary (e.g. asthma) or cardiac (NYHA III or IV) disease, no M1 RCC, no history of autoimmune disease (e.g. inflammatory bowel disease), no medical or psychological impediment to probable compliance with the protocol, no prior cancer, no active or chronic infection (e.g. HIV, hepatitis), no pregnancy.

End points

The primary objective of the study was to reduce the risk of progression through adjuvant vaccination. Secondary end points were median progression-free survival, overall survival and side effects of the vaccination.

Statistical considerations

The number of necessary patients was calculated according to a phase-II study that demonstrated a 20% benefit in terms of progression-free survival in favour of the vaccine group (Repmann et al., 1997). The minimum number of evaluable patients was calculated to be 328 with alpha = 0.05 and beta = 90%. The inclusion period was estimated to be 1.5 years, the observation period 4 years and the total study period 5.5 years.

Tumour handling and vaccination

Patients undergoing radical nephrectomy had an ipsilateral regional lymphadenectomy and those with an RCC located at the upper renal pole also had an ipsilateral adrenalectomy. A specimen (10 grams) was obtained from the peripheral zone of the tumour under sterile conditions and immediately transported in a tissue culture medium to the laboratory (Repmann et al., 1997; Goldschmidt et al., 1998). The preparation of the vaccine was performed under standardized conditions (GMP) with documentation of cell number, vitality and sterile conditions (Repmann et al., 1997; Goldschmidt et al., 1998). One milliliter of the vaccine contained a lysate of 5 million cells. The vaccine was stored at minus 85°C and kept on ice during the transport from the storage area to the patient. Before intradermal injection the vaccine was brought to room temperature. Vaccination was started 4 weeks after radical nephrectomy and repeated every 4 weeks.

Follow-up

Patients were seen every 6 months for a physical examination, blood chemistry, ultrasound, chest x-ray and abdominal CT or MRT. Monitoring of the study was performed by local monitors and Quintiles Germany.

Results

General aspects

Both groups were comparable for parameters such as age, sex, tumour localization and size, tumour stage and grade and Störkel-score. The results of this interim analysis are given for the entire study group (Fig. 1),

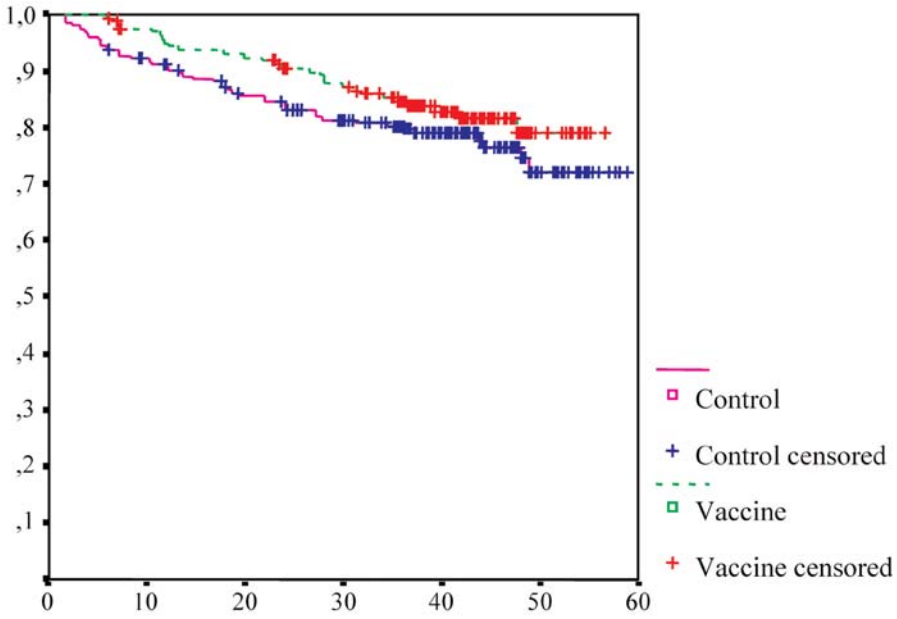

Fig. 1. Progression-free survival of patients with RCC stages **T2-3bN0-3M0**. Probability of progression-free survival on y-axis and months follow-up on x-axis. The 3-year progression-free survival rate was 80.9% in the control group compared to 84.7% in the vaccine group.

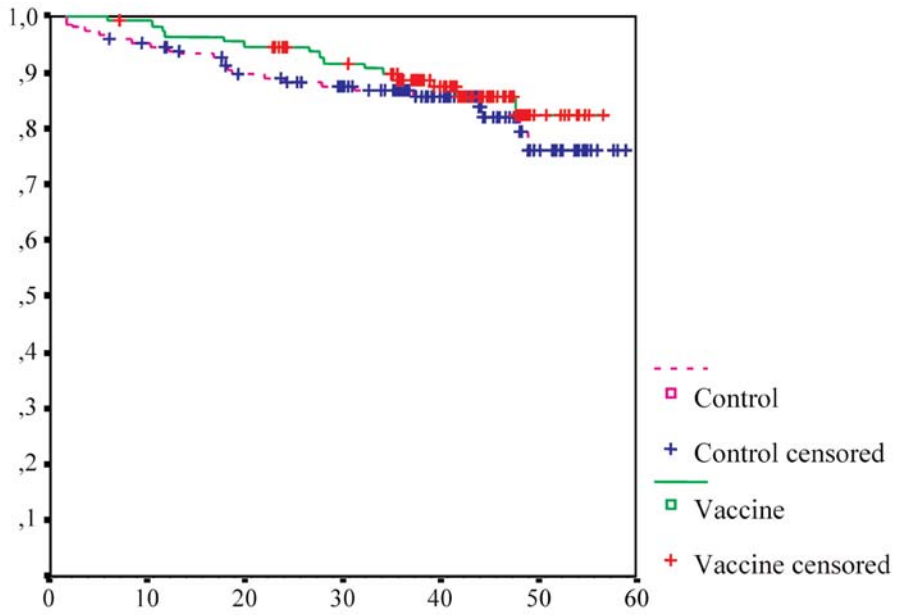

Fig. 2. Progression-free survival of patients with RCC stages **pT2pN0-3M0**. Probability of progression-free survival on y-axis and months follow-up on x-axis. The 3-year progression-free survival rate was 85.7% in the control group compared to 89.7% in the vaccine group.

patients with T2-tumours (Fig. 2), and patients with T3-tumours (Fig. 3), respectively.

Discussion

It is evident that patients with M0 RCC stages T2 or T3 do in fact have a relevant risk of progression and thus impaired survival (McNichols et al., 1981; Dal Bianco et al., 1988; Giuliani et al., 1990; Hermanek and Schrott, 1990; Dinney et al., 1992; Guinan et al., 1995; Yagoda, 1995; Jeon et al., 1999). Therefore, any attempt has to be made to reduce the risk of progression in such patients. Radical nephrectomy is obviously not radical enough and, regardless of the approach, adjuvant therapy in patients with RCC must become reality as soon as possible to eliminate distant micrometastases.

How can the risk of progression in patients with M0 RCC be reduced? Therapeutic options like radiotherapy, chemotherapy or immunotherapy are of limited or no benefit in such patients. Adjuvant radiotherapy after radical nephrectomy in patients with non-metastasized RCC has demonstrated no benefit in terms of reduction of progression rates (Finney, 1973; Kjaer et al., 1987; Makarewicz et al., 1998). There are no published studies investigating adjuvant chemotherapy in patients with RCC. In patients with M1 RCC chemotherapy demonstrated little effects due to chemotherapy resistance of the majority of RCC cells (Yagoda, 1995; Motzer and Russo, 2000). Motzer and Russo reviewed 51 phase-II studies including 1,347 patients with M1 RCC receiving chemotherapy with response rates rarely above 10% (Motzer and Russo, 2000). Adjuvant interferon-α (IFN-α) after complete resection of M0 RCC showed no benefit in reducing the rate of progression or improvement of survival of such patients (Migliari et al., 1995; Basting et al., 1999; Jeon et al., 1999; Pizzocaro et al., 2001). Interleukin-2 (IL-2) may act locally as well as systemically (Gansbacher et al., 1990). There has, however, been no phase-III study published concerning adjuvant therapy using IL-2. Thus, the standard approach for patients with M0 RCC is still the operative removal followed by watchful waiting (Motzer and Russo, 2000). Further medical therapy is only applied in case of local relapse of systemic progression (Motzer and Russo, 2000).

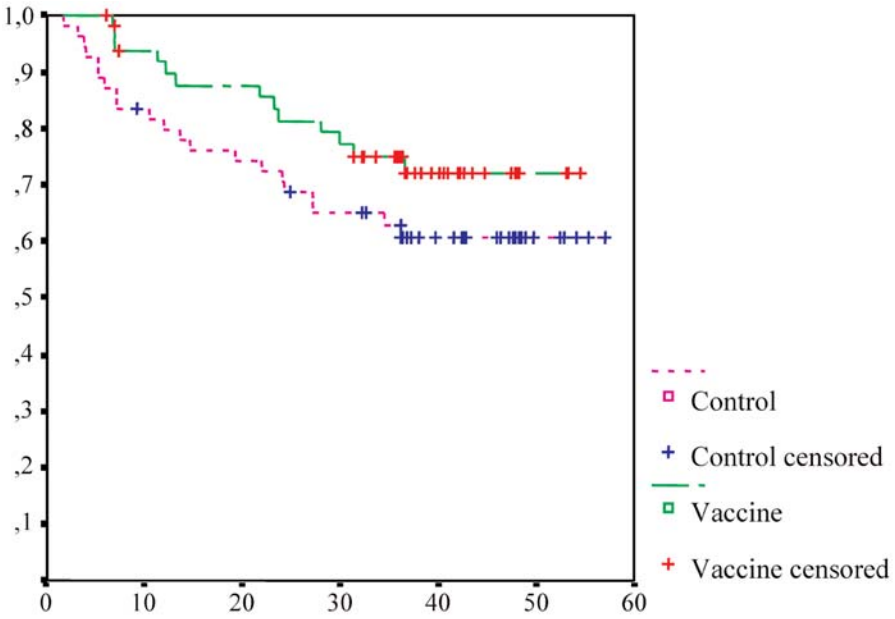

Fig. 3. Progression-free survival of patients with RCC stages **pT3pN0-3M0**. Probability of progression-free survival on y-axis and months follow-up on x-axis. The 3-year progression-free survival rate was 65.9% in the control group compared to 74.4% in the vaccine group.

Adjuvant vaccination is yet another approach in patients with RCC after radical nephrectomy. In a randomized study by Galligioni et al. it was demonstrated that tumour vaccination results in an activation of the immune system (Galligioni et al., 1996). Of 120 patients with RCC, 60 patients received a total of three intradermal vaccinations with 10^7 irradiated tumour cells. The remaining 60 patients received no adjuvant therapy. An activation of the immune system was assumed due to a positive delayed type cutaneous hypersensitivity (DTCH) response in more than 50% of vaccinated patients. However, in terms of progression-free survival and 5-year survival there were no statistically significant differences between the vaccine group and the control group (63% versus 72% and 69% versus 78%, respectively) (Galligioni et al., 1996).

Despite the presence of tumour-associated antigens and reactive T lymphocytes, the immune system is not effective in attacking tumour cells in RCC patients. The approach of tumour vaccination postulates a stimulation of the immune system of the patient. This is achieved by tumour removal and a modified antigen presentation elsewhere to the body (Rammensee, 1995; Stevanovic et al., 1995). Tumour vaccinations are based on various forms of tissue preparation, stimulation and devitalization of tumour cells as well as type and dosage of adjuvants and number of vaccine applications (Dillman et al., 1993; Kriegmair and Oberneder, 1995, Pomer et al., 1995; Repmann et al., 1997). In order to be recognized by T lymphocytes, antigens must be accessible to these cells by being presented on the cell surface of the target cell. In RCC the hypothesis is that such cells express different but yet unknown antigens compared to benign renal cells and the fact that RCC in general demonstrates a reduced expression of HLA molecules (Gansbacher et al., 1990; Boon et al., 1994). Principally, a tumour cell lysate vaccine stimulates antigen-presenting cells including dendritic cells. These cells then migrate to lymph nodes and stimulate T lymphocytes, followed by proliferation and production of cytotoxic clones to detect and destroy present tumour cells.

In the trial presented a different vaccine was used compared to the vaccines reported in the literature. This fact may have had influence on the results achieved. So far the results of this interim analysis demonstrate a difference in terms of progression-free survival in favour of the vaccine group. The advantage in terms of progression-free survival was more pronounced in patients with T3-tumours compared to T2-tumours. In this 3-year interims report we did not perform extensive statistical analysis and therefore the final report of this study (2003) must be awaited.

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