Phase 2 Study of Lutetium 177–Labeled Anti–Carbonic Anhydrase IX Monoclonal Antibody Girentuximab in Patients with Advanced Renal Cell Carcinoma

Constantijn H.J. Muselaers, Marye J. Boers-Sonderen, Tim J. van Oostenbrugge, Otto C. Boerman, Ingrid M.E. Desar, Alexander B. Stillebroer, Sasja F. Mulder, Carla M.L. van Herpen, Johan F. Langenhuijsen, Egbert Oosterwijk, Wim J.G. Oyen, Peter F.A. Mulders.

CM, TvO, AS, JL, EO, PM: Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands;

CM, TvO, OB, WO: Department of Radiology and Nuclear Medicine, Radboud, University Medical Center, Nijmegen, The Netherlands;

MBS, ID, SM, CvH: Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherland

Corresponding author: Constantijn H.J. Muselaers - Geert Grooteplein Centraal 10, 6525 GA Nijmegen, The Netherlands. Tel. +31243613735; Fax: +31 24 3541031.E-mail address: stijn.muselaers@radboudumc.nl

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Abstract

Despite advances in the treatment of metastatic clear cell renal cell carcinoma (ccRCC), there is still an unmet need in the treatment of this disease. A phase 2 radioimmunotherapy (RIT) trial with lutetium 177 (177Lu)–girentuximab was initiated to evaluate the efficacy of this approach. In this nonrandomized single-arm trial, patients with progressive metastatic ccRCC who met the inclusion criteria received 2405 MBq/m2 of 177Lu-girentuximab intravenously. In the absence of persistent toxicity and progressive disease, patients were eligible for retreatment after 3 mo with 75% of the previous activity dose. A total of 14 patients were included. After the first therapeutic infusion, eight patients (57%) had stable disease (SD) and one (7%) had a partial regression. The treatment was generally well tolerated but resulted in grade 3–4 myelotoxicity in most patients. After the second cycle, continued SD was observed in five of six patients, but none were eligible for retreatment due to prolonged thrombocytopenia. In conclusion, RIT with 177Lu-girentuximab resulted in disease stabilization in 9 of 14 patients with progressive metastatic ccRCC, but myelotoxicity prevented retreatment in some patients.

Patient summary: We investigated the efficacy of lutetium 177–girentuximab radioimmunotherapy in patients with metastatic kidney cancer. The treatment resulted in disease stabilization in 9 of 14 patients. The main toxicity was prolonged low blood cell counts.

Trial registration: ClinicalTrials.gov identifier: NCT02002312 (https://clinicaltrials.gov/ct2/show/NCT02002312)

Despite advances in the treatment of metastatic clear cell renal cell carcinoma (ccRCC) due to the advent of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) and mammalian target of rapamycin inhibitors in the past decade [1], there is still an unmet need for improved treatment options of this disease. The search for novel systemic treatment strategies with less toxicity and significant antitumor effect has led to therapeutic regimes using radiolabeled antibodies specifically targeting tumor-associated antigens expressed on tumor cells.

For ccRCC, the radiolabeled chimeric monoclonal antibody girentuximab was extensively investigated both for radioimmunodetection and radioimmunotherapy (RIT) [2–5]. Girentuximab specifically targets carbonic anhydrase IX (CAIX), a tumor-associated antigen ubiquitously expressed in primary ccRCC and its metastases but not found in the normal kidney [6]. Because of the specific targeting of girentuximab to CAIX-expressing lesions, this antibody is a potent carrier for tumor-targeted delivery of b-emitting radionuclides. In a phase 1 clinical trial, lutetium 177 (177Lu)–girentuximab RIT proved to be safe and well tolerated at activity dose levels as high as 2405 MBq/m2. Moreover, 74% of the patients with advanced ccRCC demonstrated stable disease (SD) 3 mo after the first infusion with 177Lu-girentuximab [4].

Because of these encouraging results, a nonrandomized single-arm phase 2 trial at the maximum tolerated dose was initiated to determine the therapeutic efficacy of 177Lu-girentuximab. Response was defined as at least SD on evaluation after 3 mo according to the Response Evaluation Criteria in Solid Tumors v.1.1. Secondary objectives of this study were to assess the progression-free survival (PFS) and overall survival and to explore the toxicity of the 177Lu-girentuximab treatment. Patients could receive up to three treatment cycles. Supplement 1 describes the full study materials and methods.

In total, 14 adult patients with progressive metastatic ccRCC were included between August 2011 and April 2014. Supplementary Table 1 lists the inclusion and exclusion criteria. Supplementary Table 2 summarizes patient characteristics and results.

Figure 1 shows the response of the target lesions of all patients after the first cycle of RIT. The mean growth rate of the target lesions decreased from 14% to 5%, although large differences were observed between patients. Nine of 14 patients (64%) showed a response after the first treatment cycle. Six of these nine patients were eligible for a second therapeutic infusion. The other three patients had to be excluded due to prolonged myelotoxicity. After the second RIT, durable responses were observed in five patients. None of these were eligible for a third RIT cycle due to a slow recovery from myelotoxicity. The median PFS for all patients in this study was 8.1 mo; the mean follow-up was 20 mo.

All but two patients experienced grade 3–4 thrombocytopenia in the first RIT cycle. The nadir of the platelet count was at 5 wk postinjection of 177Lu-girentuximab (Fig. 2). Patients generally recovered from grade >3 thrombocytopenia in 2–3 wk. A total of three patients developed a severe thrombocytopenia requiring thrombocyte infusion. In 10 of 14 patients, the thrombocyte count was >150 x 10^9/l at the end of the first RIT cycle; however, none of the patients reached their pre-RIT thrombocyte levels. In the seven patients receiving a second therapeutic injection, the hematologic toxicity was less severe than during the first RIT cycle. However, slow recovery from myelotoxicity precluded a third treatment cycle in five patients. Transient grade 3–4 leukocytopenia was observed in nine patients, with the nadir at a median of 6 wk after the therapeutic injection (Fig. 2). Four

patients developed grade 4 neutropenia, three of whom required hospitalization due to febrile neutropenia.

Apart from the myelotoxicity, treatment with 177Lugirentuximab was generally well tolerated; 13patients experienced mild (grade 1–2) adverse events such as fatigue, anorexia, vomiting, nausea, and diarrhea. Only two casesofgrade3adverseeventswereobserved:fatigue(n=1) and anorexia (n= 1). No allergic reactions due to the girentuximab infusions were observed. Of the six patients who were treated with VEGFR TKIs afterward, three patients could not be optimally dosed due to myelotoxicity. More data regarding the primary and secondary end points of this study are summarized in Supplement 2.

The 177Lu-girentuximab RIT resulted in stabilization of previously progressive disease in most patients with few side effects. Nevertheless, reversible grade 3–4 hematologic toxicity was observed in all but one patient, which seemed to be more profound than in the phase1 trial [4]. Because of the high incidence of grade 3–4 hematologic toxicity, in future studies the dose of 2405 MBq/m2 may have to be adjusted to allow patients to complete the three treatment cycles and allow optimal subsequent treatment with VEGFR TKIs in case of progressive disease (PD).

The results of the current study are encouraging; however, how girentuximab-based RIT should be implemented into clinical practice is not yet clear. At present, one of the biggest challenges is to identify patients who will benefit most from RIT. Previous studies indicate that RIT is mainly suitable for treatment of small-volume disease or possibly as adjuvant treatment in selected cases [7]. In the adjuvant setting, the activity dose may have to be lowered to prevent severe myelotoxicity and permit adequate treatment with VEGFR TKIs after failure of the primary treatment.

Besides optimization of the timing of RIT in the management of ccRCC, personalized dosing based on dosimetric analysis of the data acquired during the pretreatment imaging is likely to improve 177Lu-girentuximab RIT [8,9] because the trade-off between efficacy and toxicity can be tailored to individual patients. Another important step to implement girentuximab-based RIT successfully is to determine the optimal combination with other treatment modalities. As we reported in 2014, treatment with VEGFR TKIs has a profound effect on the uptake of 111In-girentuximab in ccRCC lesions [10]. Further studies are warranted to evaluate the duration of these effects induced by VEFGR TKI and could help to improve treatment strategies for metastatic ccRCC.

In conclusion, 177Lu-girentuximab RIT is promising in terms of clinical response in patients with progressive metastatic ccRCC.

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FIGURES

Fig. 1 – Tumor growth of the target lesions after radioimmunotherapy (RIT) 1 and 2 per patient according to Response Evaluation Criteria in SolidTumors v.1.1. The dotted lines in patients 3, 6, 7, 8, 11, and 14 represent the growth of the target lesions after exclusion from additional RIT cycles. CT = computed tomography; 177Lu = lutetium 177; RIT = radioimmunotherapy.

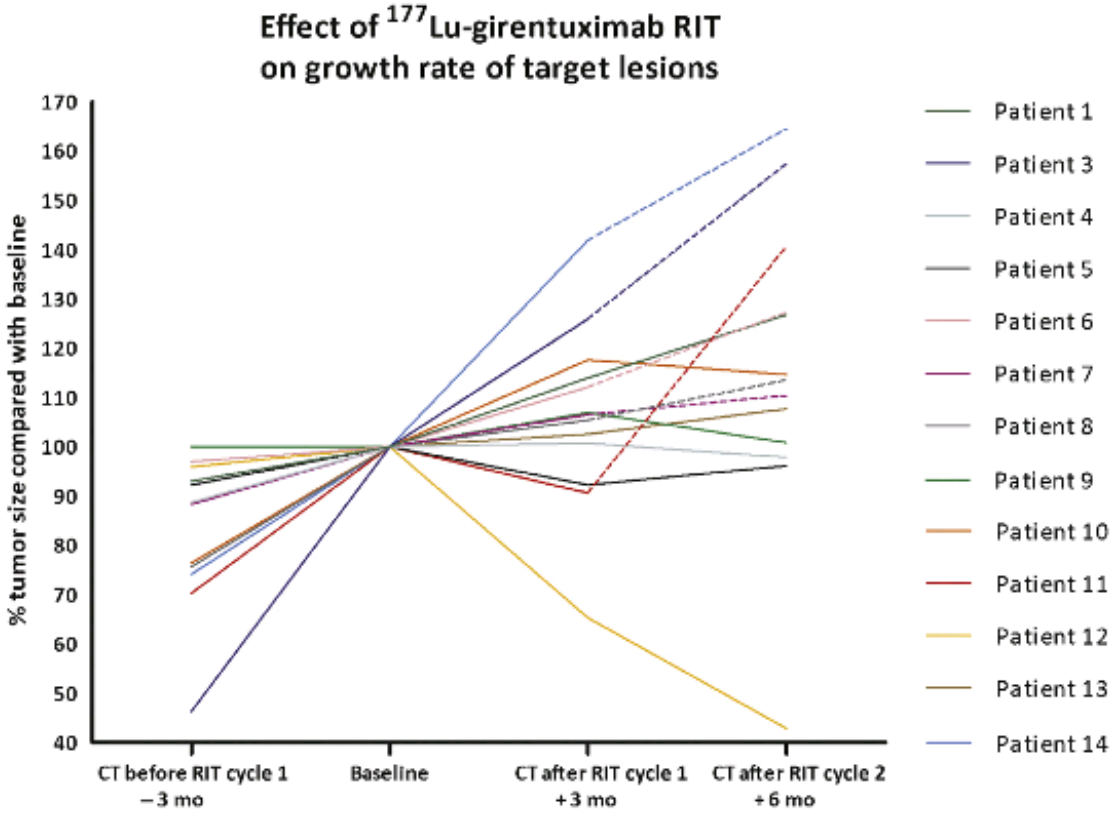

Fig. 2 – Hematologic toxicity during radioimmunotherapy 1 and 2. Thrombocyte and leucocyte counts are presented as mean plus or minus standard error of the mean. RIT = radioimmunotherapy; SEM = standard error of the mean.