Response to [^{90}Yttrium-DOTA]-TOC Treatment is Associated with Long-term Survival Benefit in Metastasized Medullary Thyroid Cancer: A Phase II Clinical Trial

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Abstract

Purpose: We aimed to explore the efficacy of ^{90}Yttrium–1,4,7,10-tetra-azacyclododecane *N,N′,N″,N-‴*-tetraacetic acid (^{90}Y-DOTA)–Tyr^3-octreotide (TOC) therapy in advanced medullary thyroid cancer.

Experimental Design: In a phase II trial, we investigated the response, survival, and long-term safety profile of systemic [^{90}Y-DOTA]-TOC treatment in metastasized medullary thyroid cancer. Adverse events were assessed according to the criteria of the National Cancer Institute. Survival analyses were done using multiple regression models.

Results: Thirty-one patients were enrolled. A median cumulative activity of 12.6 GBq (range, 1.7-29.6 GBq) of [^{90}Y-DOTA]-TOC was administered. Response was found in nine patients (29.0%). Four patients (12.9%) developed hematologic toxicities and seven patients (22.6%) developed renal toxicities. Response to treatment was associated with longer survival from time of diagnosis (hazard ratio, 0.20; 95% confidence interval, 0.05-0.81; $P = 0.02$) and from time of first [^{90}Y-DOTA]-TOC therapy (hazard ratio, 0.16; 95% confidence interval, 0.04-0.63; $P = 0.009$). The visual grade of scintigraphic tumor uptake was not associated with treatment response or survival.

Conclusions: Response to [^{90}Y-DOTA]-TOC therapy in metastasized medullary thyroid cancer is associated with a long-term survival benefit. Treatment should be considered independently from the result of the pretherapeutic scintigraphy.

No systemic therapy has been established for metastasized medullary thyroid cancer (1). Treatment with Adriamycin, cyclophosphamide, vincristine, dacarbazine, 5-fluorouracil, or combined regimes have shown only minor responses with considerable hematologic, nephrologic, cardiologic, or gastrointestinal toxicities (2, 3). On the other hand, preliminary studies revealed encouraging results with radiolabeled anti–carcinoembryonic antigen antibodies (4) and metaiodobenzylguanidine (5).

Systemic treatment with the ^{90}Yttrium (^{90}Y)-labeled, 1,4,7,10-tetra-azacyclododecane *N,N′,N″,N-‴*-tetraacetic acid (DOTA)–modified somatostatin analogue Tyr^3-octreotide (TOC) was introduced in 1998 (6). [^{90}Y-DOTA]-TOC is administered i.v. and binds to the somatostatin receptor subtype 2, located on the surface of the tumor cell, and exerts its cytotoxic effects by β-irradiation. The treatment has moderate acute hematologic and nephrologic toxicity and has developed into a promising therapeutic tool for tumors expressing its target receptor (7–9). Among other neuroendocrine tumors, medullary thyroid carcinomas express the somatostatin receptor subtype 2, which was initially used for tumor imaging (10). Pilot studies have provided proof of principle that [^{90}Y-DOTA]-TOC treatment could achieve remissions in progressive medullary thyroid cancer (11, 12). Herein, we investigated the long-term efficacy and toxicity of [^{90}Y-DOTA]-TOC treatment in medullary thyroid cancer.

Materials and Methods

Trial design. In a clinical phase II, single-center, open-label trial, we investigated the response, survival, and safety profile of [^{90}Y-DOTA]-TOC treatment in progressive metastasized medullary thyroid cancer. Adverse events were assessed according to the criteria of the National Cancer Institute. Predictors for survival were examined among the participant's baseline characteristics and the intensity of treatment. The study was designed and carried out in accordance with good clinical practice guidelines, Swiss drug laws, and the Declaration of Helsinki. The study was approved by the local ethics committee for human studies (The Ethics Committee of Basel, reference no. M120/97)[7] and written informed consent was obtained from all participants.

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[7] http://www.ekbb.ch

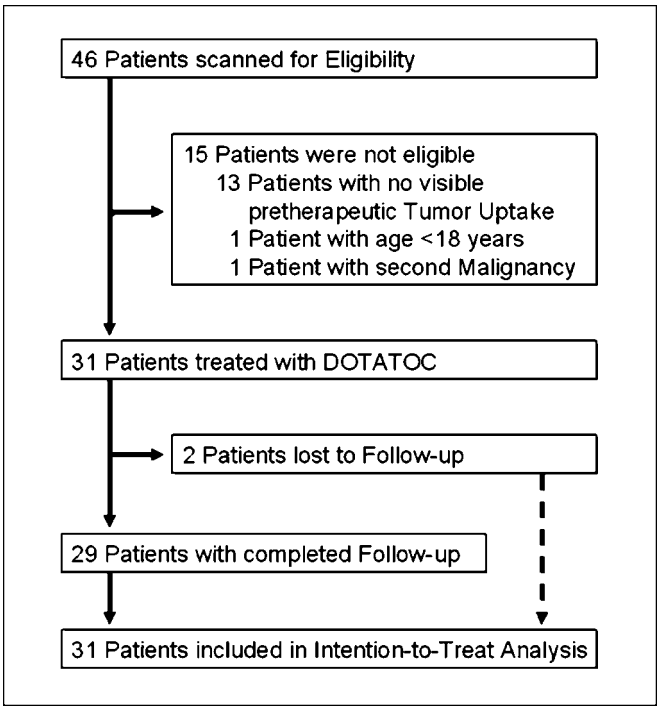

Fig. 1. Trial profile.

Trial cohort. We consecutively included patients with (*a*) histologically confirmed medullary thyroid cancer, (*b*) stage IVc disease by definition of the American Joint Committee on Cancer, i.e., occurrence of distant metastases, (*c*) disease progression within 12 months before study entry as defined by increasing calcitonin levels, and (*d*) visible tumor uptake in the pretherapeutic somatostatin receptor subtype 2 scintigraphy (^{111}In-Octreoscan). We excluded patients in case of (*a*) age younger than 18 years, (*b*) concurrent antitumor treatment, (*c*) secondary malignancies, (*d*) pregnancy, (*e*) breast-feeding, (*f*) incontinence, (*g*) severe concomitant illness including severe psychiatric disorders, or (*h*) reduced kidney function, assessed by creatinine clearance according to Cockcroft and Gault (13).

Pretherapeutic somatostatin receptor subtype 2 scintigraphy. The severity of tumor uptake in the pretherapeutic ^{111}In-Octreoscan was visually graded by a panel of two board-certified nuclear medicine physicians blinded to the patients characteristics using a four-point scale: (0) no uptake present, (1) uptake present but lower than liver uptake, (2) similar to liver uptake, and (3) higher than liver uptake.

Therapeutic radiopeptide. DOTA-TOC was synthesized in a five-step synthetic procedure according to Good Laboratory Practices as previously described (6–8). For radiolabeling, kits containing 220 μg of DOTA-TOC, 18.3 mg of ascorbic acid, and 160 mg of sodium ascorbate were labeled with 3.7 GBq/m^2 body surface ^{90}Y (β-emission for therapeutic purposes; Perkin-Elmer Life Sciences) and 0.111 GBq of ^{111}Indium chloride (γ-emission for intratherapeutic imaging; Mallinckrodt Medical). The solution was heated at 95°C for 25 min and quality control was done using solid phase extraction (Sep-Pak C18 cartridge, Waters Associates, Inc.) and high-performance liquid chromatography, with a minimum required labeling yield of >99.5%.

Radiopeptide treatment. A fractionated treatment protocol was done with i.v. injections of 3.7 GBq/m^2 body surface [^{90}Y-DOTA]-TOC per cycle as previously described (6–8). For each cycle, patients were hospitalized for 3 days in accordance with the local Swiss requirements for legal radiation protection. An infusion of 2,000 mL of Hartmann-Hepa 8% amino acid solution (Ringer Lactate Hartmann, Proteinsteril Hepa 8%, Mg 5-Sulfat) was started 30 min before and continued until 3 h after the injection of the radiopeptide to inhibit the tubular

Table 1. Patients' characteristics

Characteristic	Finding	All patients (*N* = 31)	Responders (*n* = 9)	Nonresponders (*n* = 22)	*P**
Gender	Females	10 (32%)	2 (22%)	8 (36%)	0.68
	Males	21 (68%)	7 (78%)	14 (64%)	
Age (y)	Median (range)	56.7 (24.0-76.9)	50.2 (41.4-76.0)	57.5 (24.0-76.9)	0.51
Height (cm)	Median (range)	172 (155-193)	175 (160-186)	170 (155-193)	0.38
Weight (kg)	Median (range)	70 (46-88)	69 (60-82)	74 (46-88)	0.66
Body surface (m^2)	Median (range)	1.8 (1.4-2.2)	1.8 (1.6-2.0)	1.8 (1.4-2.2)	0.98
Cases of MEN syndrome †	MEN I	1 (3.2%)	0	1 (4.5%)	1.0
	MEN IIa	2 (6.5%)	0	2 (9.1%)	1.0
	MEN IIb	0	0	0	1.0
Duration of disease (y) ‡	Median (range)	4.0 (0.1-30.8)	1.9 (0.3-13.4)	4.5 (0.1-30.8)	0.51
Pretreatment	Radioiodine	3	2	1	0.19
	Radiation	10	3	7	1.0
	Embolization	3	1	2	1.0
	Chemotherapy	8	2	6	1.0
Calcitonin (pg/mL)	Median (range)	7,553 (39-61,467)	19,700 (141-61,467)	4,471 (39-40,000)	0.16
Creatinine (μmol/L)	Median (range)	69 (27-115)	73 (60-94)	64 (27-115)	0.19
Creatinine clearance (mL/min/1.73 m^2)	Median (range)	96.3 (45.1-171.0)	94.4 (53.9-132.7)	99.1 (45.1-171.0)	0.48
Leukocytes (×10^9/L)	Median (range)	6.8 (3.5-13.3)	6.7 (4.5-12.8)	6.8 (3.5-13.3)	0.98
Platelets (×10^9/L)	Median (range)	274 (121-863)	313 (223-450)	260 (121-863)	0.06
Hemoglobin (g/dL)	Median (range)	11.5 (6.9-17.2)	11.5 (8.8-17.2)	11.5 (6.9-15.2)	0.56
Scintigraphic uptake	0	0	0	0	0.83
	1	18 (54.8%)	5 (55.5%)	13 (54.5%)	
	2	5 (16.1%)	2 (22.2%)	3 (13.6%)	
	3	8 (25.8%)	2 (22.2%)	6 (27.3%)	
Cumulative activity (GBq)	Median (range)	12.6 (1.7-29.6)	14.8 (3.4-15.7)	12.2 (1.2-13.3)	0.12

NOTE: The respective reference ranges are: calcitonin, <50 pg/mL; creatinine, 60-117 μmol/L; leukocytes, 3.5-10.0 × 10^9/L; platelets, 150-450 × 10^9/L; hemoglobin, 14.0-18.0 g/L.

*Refers to responders versus nonresponders.

† Multiple endocrine neoplasia syndrome.

‡ At time of [^{90}Y-DOTA]-TOC treatment.

reabsorption of the radioactive tracer. Repeated treatment cycles were intended for responders, except in case of renal toxicity, loss of patient transferability, or denial of further treatment. Conversely, further cycles were withheld in all nonresponders, except in patients that described a significant gain in quality of life after therapy.

Intratherapeutic imaging. Planar imaging was done with a dual-head Picker Prism 2000 XP camera (Philips) using parallel-hole, medium-energy, general-purpose collimators. The windows were centered over both ^{111}Indium photon peaks (245 and 172 keV) with a window width of 20%. Whole-body scans and spot images were obtained 24 and 48 h after application of the radionuclide with an acquisition time of 15 min.

Follow-up. Vital signs were monitored before and for 72 h after each infusion. Blood chemistry variables (including serum calcitonin and creatinine levels) and hematologic variables (including leukocytes and platelet counts and serum hemoglobin levels) were measured before each treatment cycle and in a biweekly interval until 10 weeks after each cycle or normalization of marker levels, respectively. All observed toxicities were recorded continuously. Acute and long-term adverse events were graded according to the Common Terminology Criteria for Adverse Events version 3.0[8] of the National Cancer Institute as follows. (1) Nausea: grade 1, loss of appetite without alteration in eating habits; grade 2, oral intake decreased without significant weight loss, dehydration, or malnutrition; intravenous fluids indicated <24 h; grade 3, inadequate oral caloric or fluid intake, intravenous fluids, tube feedings, or TPN indicated ≥24 h; grade 4, life-threatening consequences; grade 5, death. (2) Leukopenia [leukocytes ($\times 10^9$/L)]: grade 1, 3.5 to 3.0; grade 2, 3.0 to 2.0; grade 3, 2.0 to 1.0; grade 4, <1.0; grade 5, death. (3) Thrombopenia [platelets ($\times 10^9$/L)]: grade 1, 150.0 to 75.0; grade 2, 75.0 to 50.0; grade 3, 50.0 to 25.0; grade 4, <25.0; grade 5, death. (4) Anemia [hemoglobin (g/dL)]: grade 1, 14.0 to 10.0; grade 2, 10.0 to 8.0; grade 3, 8.0 to 6.5; grade 4, <6.5; grade 5, death. (5) Renal adverse event [creatinine clearance (mL/min/1.73 m^2)]: grade 1, <75% to 50% of the lower limit of the normal; grade 2, <50% to 25% of the lower limit of the normal; grade 3, <25% of lower limit of the normal, chronic dialysis not indicated; grade 4, chronic dialysis or renal transplant indicated; grade 5, death. The age-related reference ranges for creatinine clearance were derived from the Guidelines of the National Kidney Foundation.[9]

End points. Primary end points were treatment response and toxicity; the secondary end point was overall survival. Only patients with increasing calcitonin levels had been enrolled. In an initial analysis, response was defined as posttherapeutic prolongation of calcitonin doubling time of at least 100% (4), which however, depends on thorough measurements prior to enrollment. Thus, for calculation of the final multiple regression model, from those patients who experienced posttherapeutic prolongation of calcitonin doubling time, we defined responders only as those with decreasing calcitonin levels after therapy. The overall response rate was defined as the number of participants with response divided by the total number of participants on the basis of intention-to-treat, whereas loss of follow-up was regarded as treatment failure. Overall survival was assessed for both time from diagnosis and time from first [^{90}Y-DOTA]-TOC treatment, respectively, to death of any cause. If death did not occur during the observation period, survival time was censored at the last date the respective subject was known to be alive.

Statistical analysis. The baseline characteristics of responders and nonresponders to [^{90}Y-DOTA]-TOC were compared using the χ^2 test and Kruskal-Wallis one-way ANOVA, as appropriate. Discrete variables are summarized by counts (percentages) and continuous variables by their median (range), unless stated otherwise. The influence of different variables on the response to [^{90}Y-DOTA]-TOC was assessed using simple logistic regression models and the corresponding effect estimates were expressed as odds ratios with 95% confidence intervals. Predictors of survival from both, time of diagnosis and time of first [^{90}Y-DOTA]-TOC treatment, were initially assessed using simple proportional hazard models. Subsequently, backward selection from an initial multiple proportional hazard model including age, response, and all (other) previously significant variables led us to our final model. The corresponding effect estimates were expressed as hazard ratios with 95% confidence intervals. For quantitative covariates (e.g., baseline calcitonin, baseline serum creatinine clearance, and cumulative activity of [^{90}Y-DOTA]-TOC), we assessed whether the variable itself or its logarithmic transform was more strongly associated with the outcome variable. For all end points, sensitivity analyses were done in the subsets of responders and nonresponders to [^{90}Yttrium-DOTA]-TOC therapy. Time to event data were plotted using Kaplan-Meier curves. All P values are two-sided and $P < 0.05$ was considered to be statistically significant. Data were analyzed using Statistica V.6.0 software for Windows (StatSoft, Inc.) and SAS release 9.1 (SAS Institute, Inc.).

Results

Patients. Between October 1997 and October 2006, 46 patients were screened for eligibility. Of these, 15 patients

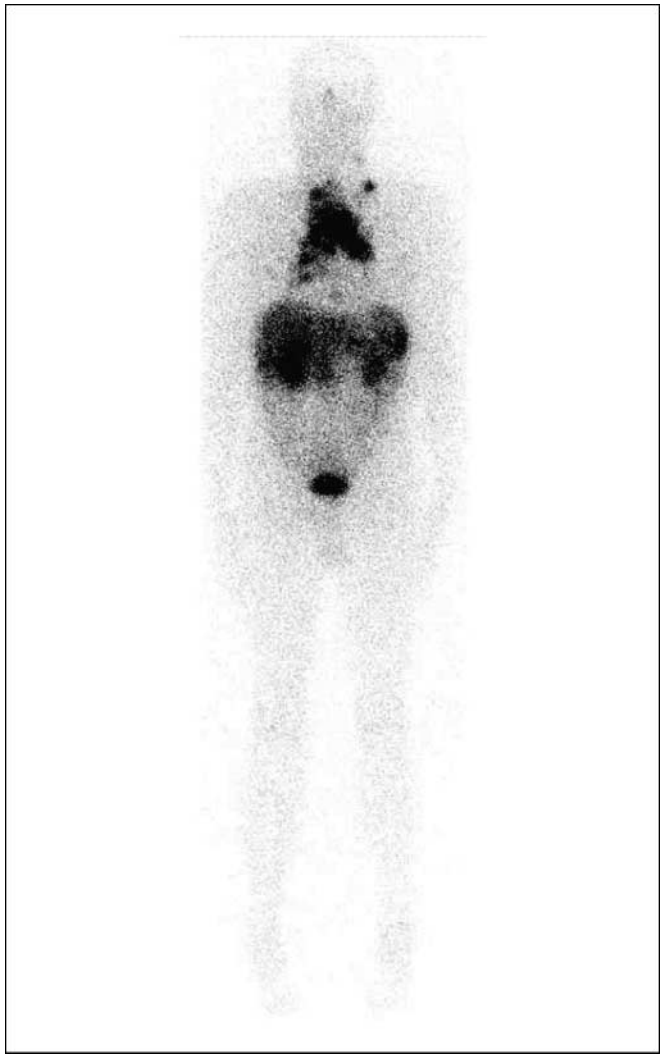

Fig. 2. Intratherapeutic scintigraphy displaying supraclavicular grade 3 [^{90}Y-DOTA]-TOC uptake in the mediastinum and in both pulmonal hili.

[8] http://ctep.cancer.gov/forms/CTCAEv3.pdf
[9] http://www.kidney.org/

Table 2. Risk factors for response and survival after [^{90}Y-DOTA]-TOC treatment

End point	Risk factor (unit)	Odds ratio (unadjusted)	P
Response to [^{90}Y-DOTA]-TOC therapy	Age (y)	1.02 (0.96-1.08)	0.56
	Sex	0.50 (0.08-3.01)	0.45
	Duration of disease (y)	1.06 (0.89-1.27)	0.51
	Calcitonin (pg/mL)	1.00 (0.98-1.02)	0.90
	Visual score	1.02 (0.41-2.53)	0.96

End point	Risk factor (unit)	Hazard ratio (unadjusted)	P	Hazard ratio (adjusted)*	P
Survival from time of diagnosis	Duration of disease (y)	0.74 (0.63-0.87)	0.0003	0.64 (0.51-0.81)	0.0003
	Response	0.50 (0.16-1.51)	0.22	0.20 (0.05-0.81)	0.02
	Age (y)	0.99 (0.96-1.03)	0.60	0.97 (0.93-1.01)	0.09
	Cumulative activity (GBq) †	0.34 (0.13-0.86)	0.02	0.45 (0.17-1.19)	0.11
	Calcitonin (ng/mL)	1.01 (0.99-1.02)	0.32		
	Sex	0.67 (0.24-1.80)	0.43		
	Kidney toxicity	1.36 (0.49-3.78)	0.56		
Survival from first [^{90}Y-DOTA]-TOC therapy	Calcitonin (ng/mL)	1.01 (1.00-1.03)	0.03	1.02 (1.00-1.04)	0.007
	Kidney toxicity	0.56 (0.19-1.70)	0.31	1.02 (1.00-1.04)	0.007
	Cumulative activity (GBq) †	0.41 (0.17-0.97)	0.04	0.24 (0.09-0.69)	0.008
	Response	0.18 (0.05-0.61)	0.006	0.16 (0.04-0.63)	0.009
	Age (y)	0.98 (0.94-1.02)	0.31	0.96 (0.93-1.00)	0.02
	Duration of disease (y)	1.05 (0.97-1.14)	0.23		
	Sex	0.85 (0.30-2.44)	0.77		
Time to kidney toxicity	Calcitonin (ng/mL)	1.01 (0.99-1.03)	0.26		
	Age (y)	1.04 (0.96-1.12)	0.34		
	Duration of disease (y)	0.89 (0.67-1.18)	0.41		
	Creatinine clearance (mL/min)	0.99 (0.96-1.02)	0.47		
	Sex	0.50 (0.04-6.11)	0.59		
	Cumulative activity (GBq) †	1.16 (0.30-4.46)	0.83		

NOTE: 95% confidence intervals are presented in parentheses.
*Adjusted for all other covariates in the list.
† Natural logarithm of cumulative activity.

(32.6%) were not enrolled because of absent tumor uptake at pretherapeutic scintigraphy (n = 13), age younger than 18 years (n = 1), or secondary malignancy (B-cell non–Hodgkin lymphoma, n = 1). The remaining 31 patients (67.4%) were recruited (Fig. 1). The participants were transferred from Germany (n = 15), Switzerland (n = 9), United States (n = 2), France (n = 2), Denmark (n = 2), and Hungary (n = 1), their baseline investigation results are shown in Table 1.

Treatment response. A total of 78 treatment cycles (one to five cycles per patient) were done with a median cumulative activity of 12.6 GBq (range, 1.7-29.6 GBq). Intratherapeutic scintigraphy revealed grade 3 visual scintigraphic tumor uptake in eight patients (25.8%; Fig. 2). A posttherapeutic prolongation of calcitonin doubling time of at least 100% was found in 18 of 31 participants (58.1%). Among these, decreasing calcitonin levels upon treatment with [^{90}Y-DOTA]-TOC were found in nine participants (29.0%). In these responders, the median reduction of serum calcitonin was 45.2% (range, 0.4-96.3%). The 9 responders and the 22 nonresponders displayed comparable baseline criteria, including the visual grade of tumor uptake in the pretherapeutic ^{111}In-Octreoscan (Table 1). Multiple regression analyses did not reveal any significant pretherapeutic predictor of treatment response (Table 2). In the nine responders, treatment was subsequently withheld after one (one case), two (one case), three (three cases), or four (four cases) cycles for lack of further response (six cases, 66.7%), kidney toxicity (two cases, 22.2%), or loss of patient transferability (one case, 11.1%).

Survival. The median follow-up period was 12.1 months (range, 1.4-107.0 months). Twenty-one participants (67.7%) had died, eight (25.8%) had survived, and two (6.5%) were lost to follow-up (one responder after 7 months, one nonresponder after 1 month). The median survival was 91 months (range, 2.2-373.1 months) from the time of diagnosis and 15.7 months (range, 1.4-107.0 months) from the time of first [^{90}Y-DOTA]-TOC treatment. Responders had a significantly longer median survival as compared with nonresponders, from time of diagnosis (108.8 months; range, 18.0-188.0 versus 80.4 months; range, 2.2-373.1; P = 0.009; Fig. 3A) and time of [^{90}Y-DOTA]-TOC treatment (74.5 months, range, 15.7-107.0 versus 10.8 months; range, 1.4-85.0, P = 0.02; Fig. 3B). Furthermore, consistent with the literature (14), increased age at the time of diagnosis was also a significant risk factor for survival (P = 0.008) in our cohort. Finally, intensified treatment with higher cumulative activities of [^{90}Y-DOTA]-TOC were associated with trends towards longer survival from time of [^{90}Y-DOTA]-TOC treatment (P = 0.007) and from time of diagnosis (P = 0.11). Figure 4A illustrates the survival of patients correlated to the cumulative administered activity of [^{90}Y-DOTA]-TOC. The detailed results of the

multiple regression analyses for risk factors of survival are shown in Table 2.

Acute toxicity. Grade 1 nausea occurred in five participants (16.1%), grade 2 to 5 nausea did not occur. Three patients (9.7%) developed grade 2 acute transient leukopenia, one patient (3.2%) developed grade 3 acute transient thrombopenia and anemia did not occur.

Long-term toxicity. Overall, six patients (19.4%) experienced renal toxicity (Fig. 4B). Transient grade 1 renal toxicity occurred in one patient 2 weeks after the first and in another patient 34 weeks after the second [^{90}Y-DOTA]-TOC treatment. No further [^{90}Y-DOTA]-TOC treatment was scheduled in both patients and renal function recovered after a period of 4 and 34 weeks, respectively. Three permanent grade 1 and one permanent grade 4 renal toxicities occurred. The grade 4 renal toxicity occurred 25.8 months after therapy, when 22 of 31 patients (71.0%) had already died. Multiple regression analysis did not reveal any significant risk factor among the patients' baseline criteria and intensity of treatment for the occurrence of renal toxicity (Table 2).

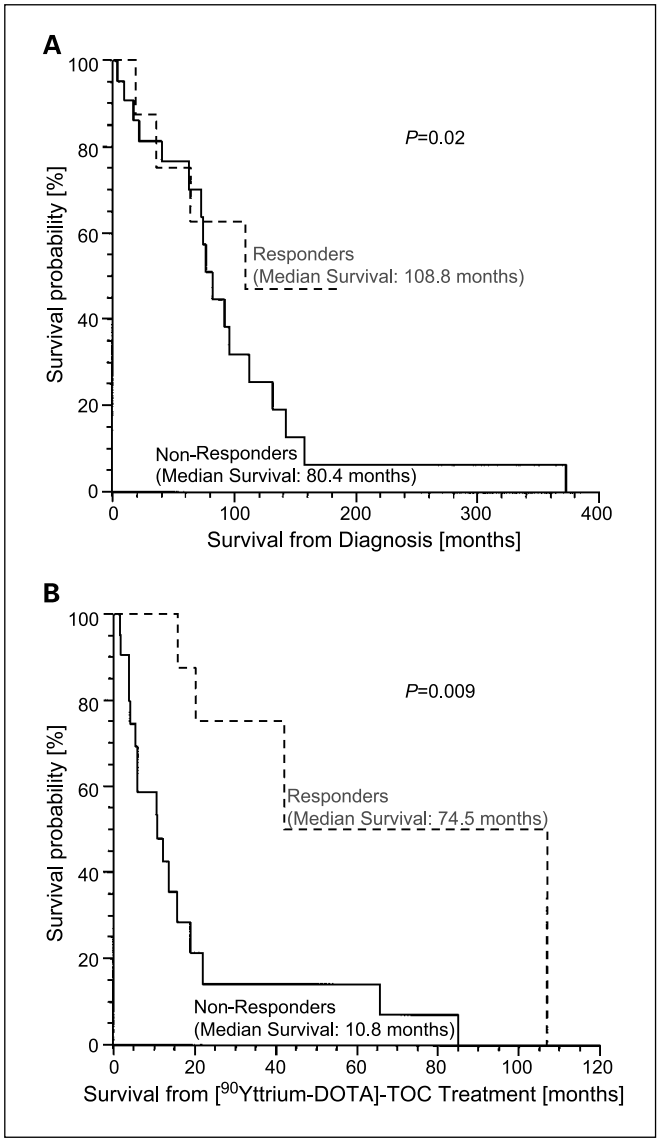

Fig. 3. Survival of responders versus nonresponders at time from diagnosis (*A*) and time from [^{90}Y-DOTA]-TOC treatment (*B*).

Discussion

In the present trial, response to [^{90}Y-DOTA]-TOC therapy in metastasized medullary thyroid cancer was associated with a long-term survival benefit. The use of [^{90}Y-DOTA]-TOC for the treatment of medullary thyroid cancer had previously been described by two pilot studies (11, 12). Both studies reported response rates comparable to our results; however, their cohort sizes and extent of follow-up were underpowered to obtain results on survival and its predictors. In contrast, the present trial revealed that response to [^{90}Y-DOTA]-TOC therapy is a decisive factor for both survival from time of diagnosis and time of recruitment, respectively. These results encourage intensifying treatment in case of response to the first cycle, especially when considering the relatively low toxicity of [^{90}Y-DOTA]-TOC treatment.

Toxicity has limited previous approaches of systemic treatment in metastasized medullary thyroid cancer. Conventional chemotherapy has shown severe toxicities with minor response and without indicators of a benefit regarding long-term survival (2, 3). Treatment with ^{131}Iodine-metaiodobenzylguanidine has shown considerable improvement in symptoms with improved quality of life (5); however, data on a potential survival benefit are thus far lacking. Pretargeted anticarcinoembryogenic-antigen radioimmunotherapy was associated with survival improvement in patients while a short calcitonin doubling time when compared with the survival of a historical cohort (4). Nevertheless, pretargeted radioimmunotherapy induced grade 4 hematologic toxicities including myelodysplasia in one-third of patients, while data on renal toxicity were not presented. In contrast, we found considerably less hematologic toxicity, comparable to previous reports (7–9), and most of our patients did not survive long enough to experience severe kidney toxicity. Additionally, kidney toxicity was not a predictor of survival after [^{90}Y-DOTA]-TOC treatment. These results again encourage intensifying treatment; especially in advanced stages of disease when a good baseline renal function is present.

Validated predictors for response to [^{90}Y-DOTA]-TOC treatment are lacking. Pretherapeutic scintigraphy is commonly used to visualize tumor uptake (10) and select cases in which successful treatment is anticipated. Accordingly, we excluded patients without visible tumor uptake for [^{90}Y-DOTA]-TOC treatment. Multiple regression analyses, however, revealed no association between pretherapeutic tumor uptake and posttherapeutic outcome. Possibly, a disseminated disease precludes scintigraphic assessment. Upcoming trials are warranted to intensify the search for alternative measures, including histologic quantification of the target receptor density and positron emission tomography with [^{68}Ga-DOTA]-TOC, to predict the response in [^{90}Y-DOTA]-TOC treatment of medullary thyroid cancer.

The most adequate method for assessing treatment response in medullary thyroid cancer also remains controversial. Morphologic imaging represents the gold standard in treatment monitoring of most malignancies (15). However, in medullary thyroid cancer, serum biomarkers have a higher sensitivity to detect tumor recurrence (16) and might also be superior in the

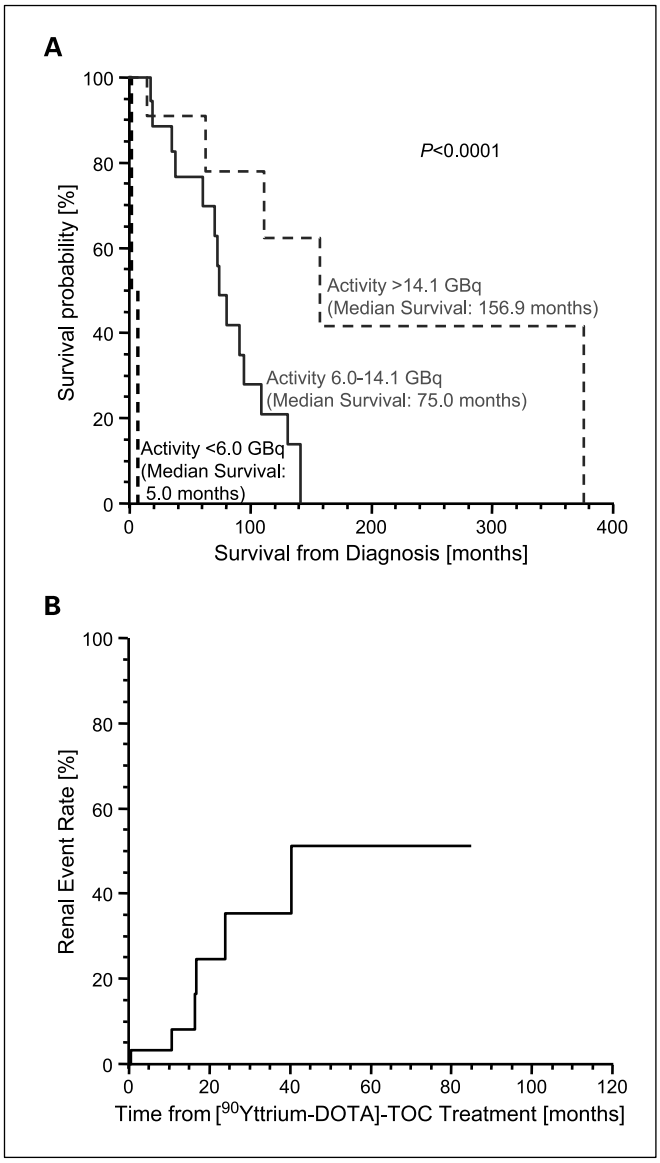

Fig. 4. Association of cumulative [^{90}Y-DOTA]-TOC activity and survival from diagnosis (*A*); renal adverse events at time from [^{90}Y-DOTA]-TOC treatment (*B*).

assessment of treatment response (17, 18). Nevertheless, calcitonin doubling time as a main outcome measure has inherent variations depending on the examined period and requires frequent and thorough measurements prior to enrollment. Thus, for the present trial, we used a more stringent definition of treatment response, i.e., not only decelerated increase of calcitonin, but a sustained decrease. Nevertheless, our results suggest the survival benefit of intensified treatment independently from achievement of response, indicating the need to evaluate better markers of treatment course in medullary thyroid cancer.

Our trial has strengths and limitations. First, the number of participants and their follow-up was sufficiently powered to obtain significant results on the prediction of survival. Nevertheless, they were derived from a single cohort and need independent confirmation to assure external validity. Second, regarding the baseline criteria, our cohort represents a wide range of clinical manifestations of medullary thyroid cancer. Therefore, we used multiple regression models and corrected all analyses for these factors. Furthermore, all survival analyses were done for both periods, time from diagnosis and from treatment, respectively. Third, statistical association does not prove causality. Other factors aside from successful treatment might have been responsible for the extended survival of treatment responders within this phase II clinical trial. A phase III placebo-controlled, randomized clinical trial is necessary to confirm a survival benefit. Finally, we were not able to define pretherapeutic markers of posttherapeutic response. The discovery of predictors remains preserved for upcoming trials. Further trials might also be warranted to investigate the effect of other radiometals, including ^{177}Lu, other somatostatin-based radiopeptides, including DOTA-TATE (19) and other radiopeptide classes, including radiolabeled gastrins (20) on the survival of patients with medullary thyroid cancer.

In conclusion, [^{90}Y-DOTA]-TOC therapy has the potential to develop into a useful tool for treating metastasized medullary thyroid cancer. According to our results, response to [^{90}Y-DOTA]-TOC in medullary thyroid cancer treatment is associated with long-term survival benefit. A randomized phase III clinical trial is warranted to confirm these results. This trial should consider patients independently from the result of pretherapeutic scintigraphy and should increase the number of treatment cycles.

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