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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Everolimus in patients with multiply relapsed or cisplatin refractory germ cell tumors: results of a phase II, single-arm, open-label multicenter trial (RADIT) of the German Testicular Cancer Study Group

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Abstract

Background Treatment options for patients (pts) with multiply relapsed or refractory metastatic germ cell cancer (GCC) are limited. The mTOR inhibitor everolimus has been approved for the treatment of different solid tumors and was assessed in refractory GCC within this phase II RADIT trial of the German Testicular Cancer Study Group.

Methods GCC pts progressing during cisplatin-based salvage chemotherapy, or relapsing after high-dose chemotherapy, or failing at least two lines of cisplatin-based chemotherapy were eligible. Prior combination chemotherapy with gemcitabine, oxaliplatin and paclitaxel, or a doublet combination of these drugs was mandatory. Primary endpoint was the progression-free survival rate at 12 weeks. Twenty-five evaluable pts were needed, assuming a 20% two-sided type 1 error and 95% power to reject the null hypothesis of 5% of patients being progression-free after 12 weeks. At least one pt among the first 13 pts being progression-free after 6 weeks was mandatory to complete recruitment. Secondary endpoints were objective response rate, disease control rate (SD + PR + CR), median progression-free survival (PFS), median overall survival (OS), and safety. The trial was registered at http://clinicaltrials.gov as NCT01242631.

Results Twenty-five pts from six German centers were treated with everolimus 10 mg orally once daily until disease progression or unacceptable toxicity between December 2010 and January 2014. 12-week PFS rate was 0%, no objective responses were achieved, and only one pt had stable disease after 6 weeks on treatment as a prerequisite of completing patient accrual accounting for a 6-week disease control rate of 5.4%. Median PFS and OS were estimated at 7.4 weeks and 8.3 weeks, respectively. Toxicity was acceptable, with one treatment discontinuation due to adverse events, and no new safety signals detected.

Conclusions Targeting the mTOR pathway with single-agent everolimus failed to produce clinically relevant responses in pts with heavily pretreated and/or cisplatin-refractory GCC.

Keywords Germ cell cancer · Testicular cancer · mTOR · Everolimus · Refractory · Cisplatin resistance

Introduction

Most patients with metastatic germ cell cancer (GCC) can be cured with cisplatin-based chemotherapy, ranging from around 60% for poor prognosis patients to > 90% for good prognosis patients (IGCCCG 1997). Unfortunately, 20–30% of patients do not respond or ultimately relapse, and only up to 50% of this subgroup of patients will achieve long-lasting remissions with multimodal salvage-treatment approaches, including high-dose chemotherapy (International Prognostic Factors Study Group et al. 2010). Objective responses with single agent salvage chemotherapy have been achieved with oral etoposide, gemcitabine, paclitaxel, and oxaliplatin (Oing et al. 2017). Remissions in refractory patients are only short lived, and the median overall survival rarely exceeds 6 months. Consequently, the investigation of new therapeutic approaches for these patients remains a high priority.

In cisplatin-resistant metastatic GCCs, overactivity of the PI3K/AKT/mTOR pathway due to a frequent loss of the tumor suppressor PTEN has been suggested to be a significant factor for tumor progression (Jacobsen and Honecker 2015; Yang et al. 2016; Hennenlotter et al. 2011; Andreassen

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et al. 2013). Everolimus is as a small molecule signal transduction inhibitor of mammalian target of rapamycin (mTOR), a key protein kinase regulating cell growth, proliferation, and survival. Interestingly, everolimus has been found to sensitize tumor cells with wild-type p53 (found in the large majority of GCCs) to apoptosis induced by cisplatin (Beuvink et al. 2005).

We, therefore, assessed the safety and efficacy of single-agent everolimus in patients with multiply relapsed or refractory GCC within a multicenter single-arm phase II trial.

Patients and methods

Patients were included in a single-arm, open-label, multicenter, phase II clinical study conducted on behalf of the German Testicular Cancer Study Group (GTCSG), recruiting patients from six hospitals in Germany. The oral mTOR inhibitor everolimus was applied at a dose of 10 mg per os daily continuously with a cycle duration of 21 days until disease progression, occurrence of unacceptable toxicity, or study discontinuation for other reasons (e.g., withdrawal of consent, protocol violation, or loss to follow-up). Dose reductions to 5 mg daily or even 5 mg every other day, and dose interruptions for up to 2 weeks were allowed in case of intolerable toxicity.

Inclusion and exclusion criteria

Male adults aged ≥ 18 years with relapsed/refractory, histologically confirmed GCC (both seminomatous and non-seminomatous), tumor progression as defined by measurable disease progression according to RECIST version 1.1 or a tumor marker increase > 25% within 4 weeks before study entry, life expectancy ≥ 3 months, Eastern Central Cooperative Group (ECOG) performance score ≤ 2 and adequate bone marrow, liver and kidney function, were eligible for study inclusion. Disease progression must have occurred during cisplatin-based chemotherapy, progression/relapse after high-dose chemotherapy, or progression/relapse after at least two different lines of cisplatin-based chemotherapy and contraindications for high-dose chemotherapy. Moreover, patients had to have received prior combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel (GOP) or prior treatment with a combination of two of these drugs if contraindications for GOP existed. Written informed consent was mandatory. Exclusion criteria were systemic antitumor treatment within less than 21 days before study entry, prior use of any mTOR inhibitor, continuous corticosteroid treatment, uncontrolled infection including hepatitis B or C, uncontrolled diabetes, history of another primary malignancy off treatment ≤ 3 years, major surgery within 4 weeks before study inclusion, and simultaneous radiotherapy of the only target lesion (incl. brain metastases).

Assessment of outcome

Disease progression and objective responses were assessed per RECIST version 1.1 by CT or MRI scan of chest and abdomen at baseline and at day 1 of the third treatment cycle (after 42 days on treatment), at the end of treatment, or at an earlier time point as clinically indicated. Tumor marker values were measured at baseline, at each respective day 1 of the next treatment cycle (i.e., at days 21, 42, etc.), and at clinical disease progression and/or end of treatment.

Progression-free survival (PFS) rate according to RECIST criteria or tumor marker measurements at 12 weeks after onset of treatment was the defined primary study endpoint. Secondary endpoints included median PFS, median overall survival (OS), objective response rate (ORR) by RECIST and tumor marker measurements, disease control rate (DCR, SD + PR + CR), safety and tolerability of the study drug.

Statistical considerations and analysis

Twenty-five evaluable patients were needed, assuming a 20% two-sided type 1 error and 95% power to reject the null hypothesis of 5% of patients being progression-free after 12 weeks. If among the first 13 patients not at least one patient had achieved a PFS of at least 6 weeks, the protocol stipulated to stop the trial for futility. Median PFS and OS were estimated according to the Kaplan–Meier method, using the R survminer (version 0.4.2) and km.ci (version 0.5–2) packages. Descriptive statistics including mean, median, range, inter-quartile range, minimum and maximum were analyzed using IBM SPSS statistics software version 22.

Toxicity and safety

Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The assessment of safety was based on the evaluation of the frequency and severity of adverse events, the number of serious adverse events (SAE), and the number of suspected unexpected serious adverse reactions (SUSAR).

All laboratory values were converted into SI (International System of Units) units. The absolute and relative number of patients with clinically relevant abnormal laboratory values are presented.

Ethical approval

The clinical trial was approved by the Ethics Committee of the Hannover Medical School and the institutional review

boards of all participating centers. The clinical trial was conducted in accordance with the ethical principles originating from the Declaration of Helsinki, consistent with Good Clinical Practice (GCP) and the applicable laws and regulations. The study was registered at http://clinicaltrials.gov, trial number NCT01242631.

Results

Study recruitment

Between December 2010 and March 2014, in total 25 GCC patients were screened, gave informed consent, were enrolled, and received at least one dose of the study drug (safety population). One additional patient was screened but did not fulfill the inclusion criteria. Twenty-two patients completed the post-baseline assessment after 12 weeks of treatment or showed disease progression or died during the first 12 weeks of treatment (intent-to-treat population). Nineteen patients showed no major protocol violations (per-protocol population), whereas three patients had major protocol violations: no previous treatment with a triple or double combination of gemcitabine, oxaliplatin and paclitaxel ($n=2$) and administration of study drug paused for more than 14 days ($n=1$).

The total study duration including the follow-up period was 39 months. Patient and disease characteristics at baseline are listed in Table 1.

Response to treatment

None of the 22 patients in the intent-to-treat population (ITT) was progression-free after 12 weeks of treatment, resulting in the primary endpoint 12-week progression-free survival rate of 0%. Outcomes for the secondary endpoints were as follows: no objective responses evaluated by radiology and tumor marker measurements were achieved

Table 1 Patient baseline disease characteristics (safety population; $n=25$)

Median age, years (range)	34.3 (21–58)
ECOG performance status, *n* (%)	
0	2 (8)
1	17 (68)
2	6 (24)
Primary site tumor, *n* (%)	
Gonadal	12 (48)
Retroperitoneal	8 (32)
Mediastinal	3 (12)
Other	2 (8)
Primary histology, *n* (%)	
Mixed germ cell cancer	2 (8)
Non-seminoma	23 (92)
Median tumor marker levels before salvage (range)	
AFP (kU/L)	10.2 (1.5–31,774.8)
βHCG (IU/L)	196.9 (0.1–92,281.0)
LDH (IU/L)	517.9 (146–2210)
Sites of metastasis at baseline, *n* (%)	
Lymph nodes	10 (40)
Lung	19 (76)
Liver	13 (52)
Brain	1 (4)
Bone	6 (24)
Prior lines of treatment, *n* (%)	
2	1 (4)
3	2 (8)
4	3 (12)
≥5	19 (76)
Prior salvage high dose chemotherapy (HD-CE), *n* (%)	22 (88)
Prior GOP triple chemotherapy, *n* (%)	17 (68)

AFP α-fetoprotein, *βHCG* β-subunit of human chorionic gonadotropin, *HD-CE* high-dose carboplatin/etoposide, *LDH* lactate dehydrogenase

(ORR, 0%). Only one patient among the first 13 recruited patients achieved a stable disease after 6 weeks, accounting for a disease control rate of 5.4% in the ITT population (also see Table 2). This allowed for complete accrual of the preplanned number of 25 patients. The median PFS and OS in the ITT population were 7.4 weeks (80% CI; 4.9–7.6 weeks), and 8.3 weeks (80% CI; 7.1–9.1 weeks), respectively. Kaplan–Meier survival curves for PFS and OS are presented in Figs. 1 and 2. The efficacy conclusions based on the per-protocol population were comparable to those of the ITT population.

Toxicity and safety analysis

All 25 patients were evaluable for safety (safety population). A total of 86 treatment-emergent adverse events (TEAEs) were reported in 16 patients (64%), of which 10 patients (40%) experienced 39 TEAEs that were considered at least possibly related to study drug administration. The most common TEAEs of all grades were dyspnea ($n=6$; 24%), anemia ($n=5$; 20%), and pain ($n=5$; 20%). TEAEs considered at least possibly related to the study drug included dyspnea (37.5%), anemia (22.5%), nausea (17.5%), and rash (15%). TEAEs grade 3–5 according to Common Toxicity Criteria (CTCAE) are listed in Table 3. The most common TEAEs grade 3–5 were pain ($n=5$, 20%) and dyspnea ($n=3$; 12%). A total number of 34 serious TEAEs were reported in 13 patients (52%). Of these, two SAEs were probably related to study drug administration: renal failure CTCAE grade 3 leading to hospitalization, study drug discontinuation and withdrawal of one patient, and dyspnea CTCAE grade 2 leading to study drug dose reduction (to 5 mg daily). Treatment interruptions occurred in two patients due to sore throat and fever, respectively. No suspected unexpected serious adverse reactions (SUSARs) were reported during the study. Moreover, there was no indication of unexpected, clinically significant changes in laboratory parameters or vital signs during treatment.

Table 2 Tumor responses (intent to treat population, $n=22$)

Complete response, *n* (%)	0 (0)
Partial response, *n* (%)	0 (0)
Stable disease, *n* (%)	1 (5)
Progressive disease (%)	21 (95)

Discussion

Preclinical data from many tumor models, including GCC, indicate that everolimus is capable to inhibit tumor cell proliferation by interrupting the PI3K/AKT/mTOR signaling cascade (Beuvink et al. 2005; Yang et al. 2016). Moreover, it's antiangiogenic properties seem to add to the anti-tumor effect indirectly. For this reason, everolimus was evaluated in relapsed and/or refractory GCC patients in this phase II clinical trial.

However, despite the preclinical rationale, efficacy of everolimus in this population was disappointing. None of the 22 patients in the ITT population reached the primary endpoint, a 12-week PFS. Moreover, survival data were

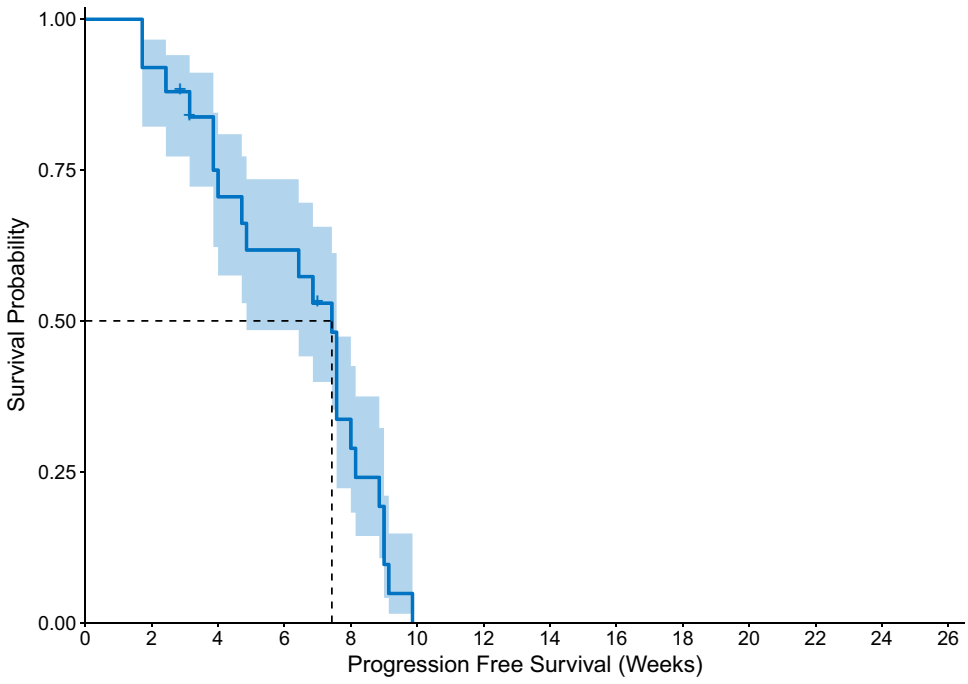

Fig. 1 Progression-free survival of entire study cohort

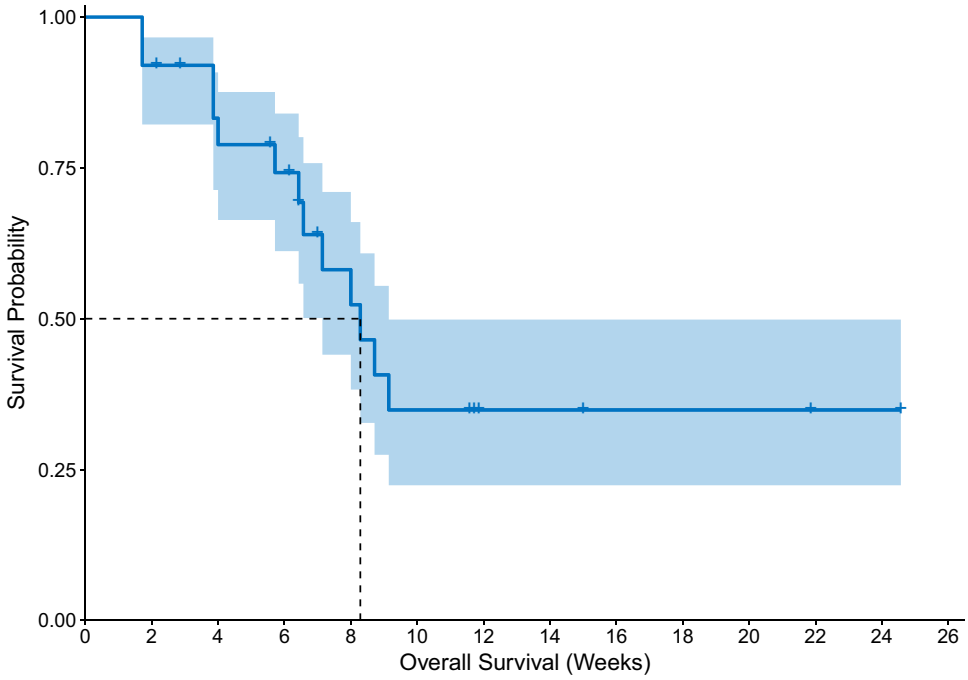

Fig. 2 Overall survival of entire study cohort

discouraging, with a median PFS of 7.4 weeks and a median OS of 8.3 weeks, respectively. The short median OS despite a life expectancy of ≥ 3 months as inclusion criterion highlights the extremely poor prognosis of refractory, heavily pretreated GCC patients. Another phase II trial from Slovenia evaluating everolimus in refractory GCC patients at the same time as our trial also failed to demonstrate significant clinical activity (Mego et al. 2016). The Slovenian study used a Simon two-stage design and was terminated prematurely after evaluation of the first 15 of the pre-planned 38 patients. The primary endpoint in that study was the objective response rate, which was 0% after the first 15 patients, instead of the required 4 out of the first 18 patients. Reported median PFS and OS were 1.7 months (95% CI 1.1–4.0 months) and 3.6 months (95% CI 2.0–11.0), respectively. Interestingly, six patients (40%) achieved a 12-week PFS, the primary endpoint of the RADIT study.

Compared to the Slovenian study population patients in the RADIT trial had more advanced GCC and had undergone more lines of treatment (≥ 3 lines: 96%, including 88% high-dose chemotherapy, vs. 53%), had to be pretreated with a double or triple drug combination of gemcitabine, oxaliplatin and paclitaxel (not required in the Slovenian study), were more likely to have primary mediastinal GCC—known to correlate with a particularly poor prognosis—(12% vs. 0%), and had to demonstrate disease progression at study entry. The remarkable difference in 12-week PFS between the two trials may, therefore, be explained by the above described differences in patient characteristics. In contrast to the Slovenian study, the RADIT study used 12-week PFS as primary study endpoint, as we assumed that everolimus was unlikely to demonstrate objective responses, based on experiences from other solid tumors (e.g., a 1% objective response rate in the RECORD-1 phase III study in advanced renal cell carcinoma; Motzer et al. 2008). Despite the identification of several 'druggable' targets in preclinical studies of GCCs, clinical trials evaluating targeted treatment approaches were often difficult to assess within clinical trials, and have so far yielded mostly disappointing results (Oing et al. 2016). The reasons for that seem to be multifaceted, i.e., (1) heavily pretreated patients due to excellent treatment options even for patients with refractory and relapsed GCC, (2) the small number of refractory GCC patients, (3) high biological heterogeneity of GCC, (4) lack of biomarkers to predict responses to targeted agents, and (5) unselected trial designs. The highest response rate reported so far was achieved with the antibody-drug conjugate brentuximab vedotin, yielding an ORR of 22% in CD30-positive GCCs. However, responses were very short lived (Necchi et al. 2016). Tyrosine kinase inhibitors, e.g., sunitinib and pazopanib, did not show clinically relevant effectiveness (Oechsle et al. 2011; Feldman et al. 2010; Necchi et al. 2017). Major responses to treatment with targeted agents are limited to case reports, and consequently no targeted therapy can be recommended, neither as a single agent, nor as part of a combination with standard cytotoxic systemic treatment, to date (Oing et al. 2016).

As a consequence, based on the negative results of clinical trials assessing targeted drugs in GCC, such as the RADIT trial, physicians should be cautioned of drawing premature conclusions from preclinical evidence towards clinical efficacy of so-called "targeted agents". This is

Table 3 Treatment-emergent adverse events (safety population; $n=25$)

System/organ class	Preferred term	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders				
	Anemia	2 (8%)		
	Thrombocytopenia	2 (8%)		
Gastrointestinal disorders				
	Abdominal distension	1 (4%)		
	Ascites	1 (4%)		
	Constipation	1 (4%)		
	Nausea	1 (4%)		
	Subileus	1 (4%)		
	Vomiting		1 (4%)	
General disorders and administrations site conditions				
	Asthenia	1 (4%)		
	Pain	2 (8%)	2 (8%)	
	Pyrexia	1 (4%)		
Hepatobiliary disorders				
	Hepatic failure			1 (4%)
	Hepatomegaly	1 (4%)		
Investigations				
	ECOG score worsened	1 (4%)		
Neoplasm benign, malignant and unspecified				
	Liver metastasis	1 (4%)		
	Neoplasm progression		1 (4%)	
	Tumor pain	2 (8%)		
Renal and urinary disorders				
	Dysuria	1 (4%)		
	Renal failure	1 (4%)		
	Urinary retention	1 (4%)		
Respiratory, thoracic and mediastinal disorders				
	Dyspnea	1 (4%)		2 (8%)
Vascular disorders				
	Hemorrhage	1 (4%)		
	Lymphedema	1 (4%)		

paramount, as taking treatment decisions to use drugs with unproven benefit in desperate treatment settings solely on the basis of genomic alterations or activated pathways is costly and potentially harmful.

Importantly, as no standard of care exists after failure of platinum-based salvage combination chemotherapy (including high-dose salvage chemotherapy with subsequent autologous stem cell transplantation), referral of such patients to expert centers to allow study participation is strongly recommended.

To conclude, single-agent treatment with everolimus failed to demonstrate meaningful clinical activity in unselected, heavily pretreated patients suffering from advanced, relapsed or refractory GCC in the RADIT single-arm phase II study.

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Compliance with ethical standards

Conflict of interest AD: honoraria for speaking at symposia by Novartis. MH: financial support by Novartis for attending symposia. CB: honoraria for speaking at symposia and refunding of travel costs by Novartis. The remaining authors (MF, CO, KO, TG, GK, FH) declare that they have no conflict of interest.

Ethical approval The RADIT trial was approved by the Ethics Committee of the Hannover Medical School and the institutional review boards of all participating centers. The clinical trial was conducted in accordance with the ethical principles originating from the 1964 Declaration of Helsinki and its later amendments, consistent with Good Clinical Practice (GCP) and the applicable laws and regulations.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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