Relevant risk of carboplatin underdosing in cancer patients with normal renal function using estimated GFR: lessons from a stage I seminoma cohort


1Oncology/Haematology, Kantonsspital Graubünden, Chur; 2SAKK (Swiss Group for Clinical Cancer Research) Coordinating Centre, Berne, Switzerland; 3Medical Oncology, Poole and Royal Bournemouth Hospitals, Bournemouth; Departments of 4Medical Oncology; 5Nuclear Medicine, University Hospital Southampton, Southampton, UK; 6Medical Oncology and Haematology, Kantonsspital St Gallen, St Gallen, Switzerland

Received 23 December 2013; revised 21 February 2014; accepted 14 March 2014

Background: Seminoma stage I is the most frequent testis cancer and single-dose carboplatin (AUC7) is an effective and widely used adjuvant treatment. Underdosing of carboplatin by 10% has been shown to almost double the rate of relapse and hence correct dosing based on accurate GFR measurement is crucial. The gold standard of GFR measurement with a radiolabelled isotope is expensive and not readily available. In many institutions, it is replaced by GFR estimation with the Cockcroft–Gault formula, which might lead to significant carboplatin underdosing and potentially inferior clinical outcome.

Methods: Retrospective analysis of all patients with stage I seminoma treated with adjuvant carboplatin between 1999 and 2012. All patients had serum creatinine measured and underwent GFR measurement with a radioisotope (51Cr EDTA or 99mTc DTPA), which was compared with seven standard GFR estimation formulae (Cockcroft–Gault, CKD-EPI, Jelliffe, Martin, Mayo, MDRD, Wright) and a flat dosing strategy. Bias, precision, rates of under- and overdosing of GFR estimates were compared with measured GFR. Bland–Altman plots were done.

Results: A total of 426 consecutive Caucasian male patients were included: median age 39 years (range 19–60 years), median measured GFR 118 ml/min (51–209), median administered carboplatin dose 1000 mg (532–1638). In comparison to isotopic GFR measurement, a relevant proportion of patients would have received ≤90% of carboplatin dose through the use of GFR estimation formulae: 4% using Mayo, 9% Martin, 18% Cockcroft–Gault, 24% Wright, 63% Jelliffe, 49% MDRD and 41% using CKD-EPI. The flat dosing strategy, Wright and Cockcroft–Gault formulae, showed the smallest bias with mean percentage error of +1.9, +0.4 and +2.1, respectively.

Conclusions: Using Cockcroft–Gault or any other formula for GFR estimation leads to underdosing of adjuvant carboplatin in a relevant number of patients with Seminoma stage I and should not be regarded as standard of care.

Keywords: seminoma stage I, adjuvant treatment, carboplatin, GFR estimation, GFR measurement

Introduction

Stage I seminoma is the most commonly diagnosed testis cancer and accounts for ~40%–45% of all testis cancers [1]. The risk of recurrence after tumour orchiectomy is 15%–20%; active surveillance or adjuvant treatment is possible management options [2]. Contemporary guidelines favour active surveillance for seminoma stage I and single-dose carboplatin is listed as adjuvant treatment option [2, 3]. The large phase III TE19/EORTC 30982 trial demonstrated the non-inferiority of a single dose of carboplatin when compared with paraaortic radiotherapy as adjuvant treatment reducing the risk of recurrence to 4%–5% [4]. Data from Scandinavia show that adjuvant carboplatin is nowadays the treatment chosen in up to 70% of all stage I seminoma patients [5]. In the phase III, TE19/EORTC 30982 trial the dosing of carboplatin was performed by using the Calvert formula with an area under the curve of 7 mg/ml/min (AUC7) [4]. The glomerular filtration rate (GFR) was determined using radioisotope measurement with either 99mTc diethylene triamine pentaacetic acid (DTPA) or 51Cr ethyldiaminetetraacetic acid (EDTA), which are both considered reference methods for measuring GFR in clinical practice [6–8]. Alternatively, collection of 24 h urine was allowed in the trial (38% of patients) but these patients received only 90% of the calculated dose according
to the TE19/EORTC 30982 protocol. In the updated analysis, these dose-reduced patients had a 5-year relapse rate of 7.4% compared with 3.9% ($P = 0.08$) for patients with adequate carboplatin dose, i.e. the rate of relapse almost doubled with only 10% dose reduction [9]. Hence, optimal dosing of carboplatin based on accurate calculation of GFR is crucial. Contrary to the pivotal trial, measurement of GFR by radioisotope scanning is uncommon in many cancer centres [10]. Using 24 h urine collection for estimation of kidney function is no longer recommended by some experts, as it is cumbersome and prone to errors [11]. Instead, estimation of GFR (eGFR) is mainly based on formulae (most commonly Cockcroft–Gault) and serum creatinine (SCrea), a practice that was explicitly not allowed in the study protocol.

The aim of this retrospective cohort analysis was to compare the actual GFR measured by radioisotope methods with different formulae for the eGFR and a proposed flat dosing algorithm in seminoma stage I patients with normal renal function and to assess their impact on potential underdosing [12].

**methods**

**patients**

All patients with stage I seminoma up to the age of 60 years treated with adjuvant carboplatin between January 1999 and January 2012 at the Cancer Care Directorates of Southampton University Hospital, Poole and Royal Bournemouth Hospitals, UK, were included. Patients were retrospectively identified from the hospital pharmacy’s chemotherapy-delivery log. Patient details including measured GFR were identified from the records of the Department of Nuclear Medicine. In a second step diagnosis, details and administration of treatment were controlled and confirmed by chart review. This enabled complete capture of all treated patients. Characteristics of each patient were recorded at the day of treatment including age, weight, height, SCrea and actual carboplatin dose administered. Body surface area (BSA) and body mass index (BMI) for each patient were calculated.

Patients exceeding the pre-defined age limit of 60 years or with incomplete datasets were excluded.

**laboratory methods**

GFR was measured by a radioisotope method ($^{99m}$Tc DTPA or $^{51}$Cr EDTA). All procedures were performed at the Nuclear Medicine Departments of Southampton University Hospital and Poole Hospital. Actual and BSA-corrected GFR values were recorded. SCrea was measured using the kinetic Jaffe method.

**GFR calculations and calculations of carboplatin dose**

Cockcroft–Gault, Jelliffe, Martin, Wright, Mayo, MDRD and CKD-EPI formulae were used for eGFR values. Actual body weight was used in all formulae and they were not corrected for standard BSA of 1.73 m$^2$. Therefore Mayo, MDRD and CKD-EPI were adjusted with the factor (BSA/1.73). Adjustment for race was not included as >95% of patients were of Caucasian origin.

Hypothetical and actual Carboplatin doses based on different GFR estimations and measured GFR were derived using the Calvert formula with an AUC7. Hypothetical Carboplatin dose was also calculated using the flat dosing formula by Ekhart et al. [12] based on mean clearance of our own patient population.

**statistical methods**

Bias for each GFR formula and hypothetical carboplatin dose compared with measured GFR and the actual Carboplatin dose was quantified by percentage error (PE %), i.e. the percentage difference between the estimated and measured GFR. Positive bias indicates overestimation of GFR, negative bias indicates underestimation.

Precision was determined by absolute percentage error (APE), i.e. the absolute difference (i.e. only positive values) between the estimated and measured GFR as percentage of measured GFR. Number and percentage of patients, who would be considered undertreated (defined as <90% of actual dose based on measured GFR) or considered overdosed (defined as >125% of actual dose) were calculated.

Bland–Altman plots illustrate bias and distribution of errors between estimated and measured GFR in relation to different levels of renal function [13].

Mean percentage error (MPE), mean absolute percentage error (MAPE) and proportion of patients with clinically relevant over- and underdosing were calculated for different subgroups according to age and BMI.

Formulae including references are listed in supplementary material S1, available at *Annals of Oncology* online.

Statistical calculations and plots were performed with R Project for Statistical Computing Software, Version 3.0.2 [14].

**results**

A total of 473 patients having received adjuvant Carboplatin AUC7 were identified. Ten patients (2.1%) over 60 years and 37 (7.8%) with SCrea analysed by external laboratories not using the kinetic Jaffe method were excluded. The patients excluded did not differ in any relevant way from those included (supplementary Table S2, available at *Annals of Oncology* online). Table 1 shows the characteristics of the 426 (90.1%) assessable patients.

**comparison of GFR and carboplatin doses**

Table 2 shows that the Cockcroft–Gault, Wright formulae and the flat dosing algorithm exhibited the least bias (MPE of +2.1, +0.4, and +1.9, respectively) and best precision (MAPE 15 and 13) with greatest proportions of potential underdosing (63% and 49%).

**Table 1. Patient demographics and clinical data**

<table>
<thead>
<tr>
<th>N = 426</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 (18–60)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85 (54–200)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.79 (1.56–2.04)</td>
</tr>
<tr>
<td>BSA (m$^2$)</td>
<td>2.03 (1.62–3.09)</td>
</tr>
<tr>
<td>Carboplatin dose AUC7 (mg)</td>
<td>1000 (532–1638)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>89 (54–136)</td>
</tr>
<tr>
<td>GFR measured (ml/min)</td>
<td>118 (51–209)</td>
</tr>
<tr>
<td>GFR normalised to BSA (ml/min/1.73 m$^2$)</td>
<td>99 (41–159)</td>
</tr>
</tbody>
</table>

Patients with normal renal function

- GFR >90 ml/min/1.73 m$^2$ 78.7% ($n = 343$)
- GFR >100 ml/min 83.7% ($n = 365$)
Martin and Mayo formulae would lead to increased overestimation (MPE +7.3 and +14, respectively) with high proportions of potentially adverse overdosing in 10% and 25% of patients.

The PEs between estimated and measured GFR are also shown as waterfall plots facilitating the visualisation of the magnitude of imprecision, the predominant direction of differences and proportions of patients with hypothetical under- and overdosing for each formula (Figure 1, supplementary Figure S3a, available at Annals of Oncology online).

Bland–Altman plots show that differences between estimated and measured GFR increase with higher GFR values for the Cockcroft–Gault and Martin formulae. This is less pronounced for the Wright and Mayo formulae. On the contrary, MDRD, Jelliffe and the CKD-EPI formulae in particular are associated with greatest negative bias and potential harmful underdosing in the adjuvant setting. This cut-off is based on a post hoc analysis of the TE19/EORTC 30982 trial showing a trend for an increased risk of relapse in those patients with seminoma stage I, who had a dose reduction by 10% (7.4% versus 3.9%; \( P = 0.08 \)) [9]. Additionally, the concept of a steep dose response in stage I and metastatic Seminoma is supported by a number of studies using Carboplatin at various dose levels [16–20].

The upper limit of a potential carboplatin dose of 125% to define potential harmful overdosing has been chosen arbitrarily based on historical comparisons from the metastatic setting: carboplatin AUC10 (\( = \)30% greater than AUC7) has been suggested as the upper limit of safe use in patients with advanced Seminoma due to grade 3 and 4 neutropenia in 54% and 24% and grade 3 thrombocytopenia in 54% [21]. In comparison, toxicity from carboplatin AUC7 was mild in the TE19/EORTC 30982 trial (12% grade 1–2 and 4% grade 3–4 thrombocytopenia) [4].

According to our analysis, CKD-EPI, MDRD and Jelliffe formulae are associated with greatest negative bias and potential overdosing in 41%, 49% and 63% of patients, respectively. In contrast, Mayo and Martin formulae have the most pronounced tendency for overestimation (MPE of +14 and +7.3). Cockcroft–Gault and Wright formulae and the modified flat dosing approach appear to have the lowest bias in our patient cohort with rates of potential overdosing of 18%, 19% and 24%. Subgroup analyses show, that patients with a BMI of 20–25 or 40–49 and MDRD or heterogeneous cohorts of cancer patients, who were often elderly and co-morbid (Jelliffe, Martin, Wright). Younger patients with testicular cancer and normal renal function were underrepresented.

Inulin clearance, which cannot be applied in clinical practice, is regarded as gold standard of GFR measurement. However, radioisotope methods have a high correlation with inulin clearance (\( r = 0.97 \)) and can therefore be regarded as the best reference method for GFR measurement in clinical practice and equal to the gold standard [15].

In our analysis, a potential carboplatin dose of \( \leq 90\% \) of the actual carboplatin dose was chosen as the cut-off value to define potential harmful underdosing in the adjuvant setting. This cut-off was based on a number of studies using Carboplatin at various dose levels [16–20].

The upper limit of a potential carboplatin dose of 125% to define potential harmful overdosing has been chosen arbitrarily based on historical comparisons from the metastatic setting: carboplatin AUC10 (\( = \)30% greater than AUC7) has been suggested as the upper limit of safe use in patients with advanced Seminoma due to grade 3 and 4 neutropenia in 54% and 24% and grade 3 thrombocytopenia in 54% [21]. In comparison, toxicity from carboplatin AUC7 was mild in the TE19/EORTC 30982 trial (12% grade 1–2 and 4% grade 3–4 thrombocytopenia) [4].

According to our analysis, CKD-EPI, MDRD and Jelliffe formulae are associated with greatest negative bias and potential overdosing in 41%, 49% and 63% of patients, respectively. In contrast, Mayo and Martin formulae have the most pronounced tendency for overestimation (MPE of +14 and +7.3). Cockcroft–Gault and Wright formulae and the modified flat dosing approach appear to have the lowest bias in our patient cohort with rates of potential overdosing of 18%, 19% and 24%. Subgroup analyses show, that patients with a BMI of 20–25 or 40–49 and MDRD or heterogeneous cohorts of cancer patients, who were often elderly and co-morbid (Jelliffe, Martin, Wright). Younger patients with testicular cancer and normal renal function were underrepresented.

Inulin clearance, which cannot be applied in clinical practice, is regarded as gold standard of GFR measurement. However, radioisotope methods have a high correlation with inulin clearance (\( r = 0.97 \)) and can therefore be regarded as the best reference method for GFR measurement in clinical practice and equal to the gold standard [15].

In our analysis, a potential carboplatin dose of \( \leq 90\% \) of the actual carboplatin dose was chosen as the cut-off value to define potential harmful underdosing in the adjuvant setting. This cut-off was based on a number of studies using Carboplatin at various dose levels [16–20].

The upper limit of a potential carboplatin dose of 125% to define potential harmful overdosing has been chosen arbitrarily based on historical comparisons from the metastatic setting: carboplatin AUC10 (\( = \)30% greater than AUC7) has been suggested as the upper limit of safe use in patients with advanced Seminoma due to grade 3 and 4 neutropenia in 54% and 24% and grade 3 thrombocytopenia in 54% [21]. In comparison, toxicity from carboplatin AUC7 was mild in the TE19/EORTC 30982 trial (12% grade 1–2 and 4% grade 3–4 thrombocytopenia) [4].

According to our analysis, CKD-EPI, MDRD and Jelliffe formulae are associated with greatest negative bias and potential overdosing in 41%, 49% and 63% of patients, respectively. In contrast, Mayo and Martin formulae have the most pronounced tendency for overestimation (MPE of +14 and +7.3). Cockcroft–Gault and Wright formulae and the modified flat dosing approach appear to have the lowest bias in our patient cohort with rates of potential overdosing of 18%, 19% and 24%. Subgroup analyses show, that patients with a BMI of 20–25 or 40–49 and MDRD or heterogeneous cohorts of cancer patients, who were often elderly and co-morbid (Jelliffe, Martin, Wright). Younger patients with testicular cancer and normal renal function were underrepresented.

Inulin clearance, which cannot be applied in clinical practice, is regarded as gold standard of GFR measurement. However, radioisotope methods have a high correlation with inulin clearance (\( r = 0.97 \)) and can therefore be regarded as the best reference method for GFR measurement in clinical practice and equal to the gold standard [15].

In our analysis, a potential carboplatin dose of \( \leq 90\% \) of the actual carboplatin dose was chosen as the cut-off value to define potential harmful underdosing in the adjuvant setting. This cut-off was based on a number of studies using Carboplatin at various dose levels [16–20].

The upper limit of a potential carboplatin dose of 125% to define potential harmful overdosing has been chosen arbitrarily based on historical comparisons from the metastatic setting: carboplatin AUC10 (\( = \)30% greater than AUC7) has been suggested as the upper limit of safe use in patients with advanced Seminoma due to grade 3 and 4 neutropenia in 54% and 24% and grade 3 thrombocytopenia in 54% [21]. In comparison, toxicity from carboplatin AUC7 was mild in the TE19/EORTC 30982 trial (12% grade 1–2 and 4% grade 3–4 thrombocytopenia) [4].

According to our analysis, CKD-EPI, MDRD and Jelliffe formulae are associated with greatest negative bias and potential overdosing in 41%, 49% and 63% of patients, respectively. In contrast, Mayo and Martin formulae have the most pronounced tendency for overestimation (MPE of +14 and +7.3). Cockcroft–Gault and Wright formulae and the modified flat dosing approach appear to have the lowest bias in our patient cohort with rates of potential overdosing of 18%, 19% and 24%. Subgroup analyses show, that patients with a BMI of 20–25 or 40–49 and MDRD or heterogeneous cohorts of cancer patients, who were often elderly and co-morbid (Jelliffe, Martin, Wright). Younger patients with testicular cancer and normal renal function were underrepresented.

Inulin clearance, which cannot be applied in clinical practice, is regarded as gold standard of GFR measurement. However, radioisotope methods have a high correlation with inulin clearance (\( r = 0.97 \)) and can therefore be regarded as the best reference method for GFR measurement in clinical practice and equal to the gold standard [15].

In our analysis, a potential carboplatin dose of \( \leq 90\% \) of the actual carboplatin dose was chosen as the cut-off value to define potential harmful underdosing in the adjuvant setting. This cut-off was based on a number of studies using Carboplatin at various dose levels [16–20].

The upper limit of a potential carboplatin dose of 125% to define potential harmful overdosing has been chosen arbitrarily based on historical comparisons from the metastatic setting: carboplatin AUC10 (\( = \)30% greater than AUC7) has been suggested as the upper limit of safe use in patients with advanced Seminoma due to grade 3 and 4 neutropenia in 54% and 24% and grade 3 thrombocytopenia in 54% [21]. In comparison, toxicity from carboplatin AUC7 was mild in the TE19/EORTC 30982 trial (12% grade 1–2 and 4% grade 3–4 thrombocytopenia) [4].

According to our analysis, CKD-EPI, MDRD and Jelliffe formulae are associated with greatest negative bias and potential overdosing in 41%, 49% and 63% of patients, respectively. In contrast, Mayo and Martin formulae have the most pronounced tendency for overestimation (MPE of +14 and +7.3). Cockcroft–Gault and Wright formulae and the modified flat dosing approach appear to have the lowest bias in our patient cohort with rates of potential overdosing of 18%, 19% and 24%. Subgroup analyses show, that patients with a BMI of 20–25 or 40–49 and
50–59 years of age are at increased risk of underdosing by the Cockcroft–Gault formula (27%, 28% and 33%). Younger or obese patients (20–29 years, BMI 30–35) seem to have a lower risk of underdosing (5% and 13%, respectively) and a modest risk of overdosing (13% and 7%) if the Cockcroft–Gault formula was used. However, we point out that the absolute number of patients included in these subgroups is rather small (n = 61 and n = 69) representing only 14.3% and 16.2% of the whole cohort. Therefore, this finding should be verified in an independent and larger cohort.

Dosing of carboplatin by the Calvert formula based on GFR has been questioned recently by Ekhart et al. [12] based on pharmacokinetic data. They proposed flat dosing of carboplatin if the average carboplatin clearance or GFR for a given population is known. As an interesting finding of our analysis this simple flat dosing algorithm performs well in comparison to the more complicated Cockcroft–Gault formula: the bias is almost identical (MPE +1.9 compared with +2.1) with only slight numerical differences for under- (19% versus 18%, respectively) and overdosing (5% versus 7%). However, this approach based on mean GFR may be ‘overfitted’ for our cohort, which at least in part explains its good performance. Flat dosing could serve as a basis for the development of a more simple and precise dosing algorithm for predefined homogeneous groups of patients. But more research into alternatives to the existing formulae should be undertaken beforehand.

Several authors have compared carboplatin dose based on GFR estimates with measured GFR in heterogeneous cohorts of varying size demonstrating varying degree of bias and imprecision for different formulae [22–26]. The largest analysis published by Ainsworth et al. [22] compared four formulae in a cohort of more than 600 oncological patients, with different cancer types, wide range of age and renal function. They demonstrate lowest bias and highest precision for the Cockcroft–Gault and Wright formulae in the subgroup of patients with BMI >30. Their analysis shares several additional similarities with our work such as a comparable magnitude of imprecision (median APE) and the phenomenon of higher underestimation of GFR by the Cockcroft–Gault formula in patients over 40 years when compared with younger than 40 [22]. Our data are in line with one conclusion of a recent paper by Dooley et al. [26] that oncology derived formulae (Martin, Wright) do not demonstrate any significant advantage over other formulae. In contrast to their work, we have chosen a more stringent cut-off

**Figure 1.** Waterfall plots: X-axis: individual patients (n = 426); Y-axis: percentage error (PE) of GFR estimation by different formulae. Dashed lines: limits of underdosing (<90% of actual target dose (ATD) and overdosing (>125% ATD)). For a comprehensive compilation of plots of all formulae, see supplementary Figure S3a, available at Annals of Oncology online.
point for underdosing (≥10% versus ≥20% below actual dose). Consequently, our data do not support the view that all bedside formulae result in similar accuracy [26]. The CKD-EPI formula in particular has the most pronounced tendency to increasingly underestimate GFR at higher levels of renal function. Conclusions derived from a ‘general oncological population’ with wide range of predominantly older age, higher percentage of impaired renal function, often treated in palliative intention have only limited validity for younger patients with normal and high GFR treated with curative intention.

Some guidelines recommend capping of GFR value in the Calvert formula at 125 ml/min [27]. However, neither the results from the TE19/EORTC 30982 trial nor our data support this practice in patients with seminoma stage I, and we clearly advise against it in the context of adjuvant treatment with carboplatin [4, 9].

Particular strengths of this current analysis include the focus on a large homogeneous patient population with predominantly normal renal function. Therefore potential of interference by other factors such as comorbidities and ageing appears low. Data have been prospectively collected in a representative routine clinical setting.

Disadvantages are the hypothetical nature making the association with clinical data impossible. Expertise to perform high-quality GFR measurements with radioisotope methods may be restricted to a limited number of centres limiting reproducibility or widespread use in clinical practice.

In summary, neither the Cockcroft–Gault formula nor other formulae for eGFR can be recommended as an alternative to radioisotope measurements based on this analysis. Certain subgroups of patients (age 40–59 years, BMI 20–25) are at particular high risk of under-treatment if eGFR by Cockcroft–Gault is used for carboplatin dosing potentially compromising clinical outcome. Oncologists treating young patients with normal renal function with carboplatin must be aware of these limitations of the formulae for GFR estimation. Consequently, radioisotope

**Figure 2.** Bland–Altman plots: X-axis: measured GFR (ml/min); Y-axis: absolute GFR difference (estimated GFR by formula – measured GFR). Bold line: mean of differences. Dashed lines: regression-based limits of agreement. For a comprehensive compilation of plots of all formulae, see supplementary Figure S3a, available at *Annals of Oncology* online.
measurement of GFR is recommended unless improvements of dosing algorithms are achieved for the use in settings and health systems where GFR measurement is impossible.

**acknowledgements**

We thank the staff from the Oncology Pharmacy of Southampton University Hospital for the great support in identification of patients.

**disclosure**

The authors have declared no conflicts of interest.

**references**


Activity and safety of RAD001 (everolimus) in patients affected by biliary tract cancer progressing after prior chemotherapy: a phase II ITMO study

R. Buzzoni¹, S. Pusceddu²*, E. Bajetta³, F. De Braud², M. Platania², C. Iannacone₄, M. Cantore⁵, A. Mambrini⁶, A. Bertolini⁶, O. Alabiso⁷, A. Ciarello⁸, C. Turco⁹ & V. Mazzaferro¹⁰

¹Day Hospital/Outpatient Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; ²Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; ³Medical Oncology Unit, Policlinico di Monza, Monza; ⁴Biostatistician LB Research srl, Cantis; ⁵Medical Oncology Unit, Azienda Ospedaliera Sondrio, Sondrio; ⁶Medical Oncology Unit, A.U.O. Maggiore della Carità, Novara; ⁷Medical Oncology Unit, Usl 4, Presidio Ospedaliero, Prato; ⁸Medical Oncology Unit, Italian Trials in Medical Oncology (ITMO) Group, Fondazione IRCCS Istituto Nazionale Tumori, Milan; ⁹Gastro-Intestinal Surgery, Liver Transplantation and Hepatology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Received 8 January 2014; revised 24 April 2014; accepted 25 April 2014

Background: Biliary tract cancer (BTC) is a highly lethal disease for which the best available therapy remains undetermined. The mammalian target of rapamycin (mTOR) pathway is up-regulated in several cancers, including BTC, and preclinical evidence indicates that mTOR inhibition may be effective in the treatment of BTC. We sought to evaluate the activity and tolerability of the mTOR inhibitor RAD001—everolimus—in patients with BTC progressing after prior chemotherapy.

Patients and methods: This was an open-label, single-arm, phase II study (EUDRACT 2008-007152-94) conducted in eight sites in Italy. Patients with locally advanced, metastatic or recurrent BTC progressing despite previous chemotherapy received a daily oral dose of everolimus 10 mg administered continuously in 28-day cycles. The two primary end