significant improvement of the symptoms (Figure 1C). Regorafenib inhibits the angiogenic and stromal receptor tyrosine kinases, vascular endothelial growth factors receptors, tyrosine kinase endothelial 2 and PDGFR-β. In colorectal cancer patients, objective responses to regorafenib have been rarely observed (1% response rate [1]). As our patient showed a response lasting over 9 months, we analyzed the patient’s tumor by NGS using targeted amplification with the AmpliSeq Comprehensive Cancer panel (Ion Torrent, Life Technologies) which includes all exons of 409 cancer genes; the amplified regions were sequenced according to [3]. Alignment, variant calling and filtering were done with Ion Reporter v4.0 (Life Technologies) and are summarized in supplementary Tables S1 and S2, available at Annals of Oncology online. We detected a nonsynonymous point mutation of PDGFR-β at codon 6 (p. A6V) which was confirmed by Sanger sequencing (Figure 2A). This mutation has already been described in the COSMIC database (ID = 1435169) as a unique case out of 367 colon carcinomas investigated. As this represents a rare mutation, we sequenced this region in the genomic DNA derived from the patient’s peripheral blood mononuclear cells and detected the same strong heterozygous signal, demonstrating this to be a germline mutation (Figure 2B). Moreover, we could exclude the presence of this mutation in the genomic DNA derived from tumor samples of four patients affected by metastatic colorectal cancer not responding to regorafenib (Figure 2C). A strong and homogenous expression of PDGFR-β could be detected in the patient’s tumor compared with the nonresponder patients (supplementary Figure S1, available at Annals of Oncology online). PDGFR and their receptors (PDGFR-α, PDGFR-β and PDGFR-αβ) play a critical role in cancer development [4, 5]. Mutations involving up-regulation of PDGF and/or PDGFR have been documented in a number of solid tumors and hematological malignancies. In colon cancer, previous reports have shown sensitivity of a cell line with mutation (p.T681I) of PDGFR-β, to sorafenib [6] and a recent case report described another germline mutation in exon 19 of PDGFR-β [7] associated with increased pathway activation and survival. To date, mutations of PDGFR-β have not been correlated to response to regorafenib, neither in cell lines nor in patients. Here we describe for the first time the germline mutation c.17C>T (NM_002609.3) of PDGFR-β, a target of regorafenib and hypothesize that this mutation, in the signal peptide of PDGFR-β, might have an oncogenic driver potential [8]. Although objective responders to regorafenib are rare, it would be of major interest to confirm this result in a larger group of patients to define if PDGFR-β is a predictive marker to this treatment.

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Pharmacokinetic interaction involving fenofibrate and everolimus

We have read with great attention the recent review by Aapro et al. [1] on the management of adverse events in cancer patients receiving everolimus. Although we agree with the authors that high levels of triglycerides increase the risk of pancreatitis, we question the opportunity of using fibrates in this setting, in view of the following observation.

A 57-year-old patient with a past history of hypertension and smoking (25 pack-years) underwent lumpectomy and axillary dissection (1N+13) for a 28-mm, grade II, hormone receptor-positive, HER2-negative, invasive ductal breast carcinoma in 2007. She subsequently received adjuvant chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide for three cycles followed by three cycles of docetaxel), radiotherapy, then anastrozole for 5 years. Seventeen months after the end of anastrozole, metastatic bone disease was diagnosed. She was prescribed exemestane 25 mg and everolimus 10 mg daily [2]. At this time, her liver function tests, cholesterolemia and triglyceridemia were normal. Her co-medications were zoledronic acid, bromazepam and losartan.

The combination of exemestane and everolimus was well tolerated, with grade 2 stomatitis being the worst toxicity. After 1 month of treatment, she developed grade 1 hypercholesterolemia (280 mg/dl) and grade 2 hypertriglyceridemia (480 mg/dl), and was therefore started on fenofibrate 160 mg/day by her treating physician. Everolimus trough plasma concentration was 10.1 ng/ml (within the range described in the phase I trial at this dosage [3]) before introduction of fenofibrate. Two weeks later, stomatitis had regressed, but everolimus trough concentration

References


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had dropped to 4.2 ng/ml. Fenofibrate is known to induce the activity of CYP3A4 [4], the main metabolic pathway for everolimus [3], with previously documented impact on the pharmacokinetics and activity of erlotinib, another substrate of CYP3A4 [4]. Hence, fenofibrate was withdrawn. Two weeks later, everolimus trough concentration rose up to 11.5 ng/ml, and stomatitis (grade 1) had recurred. She remains under everolimus and exemestane, with stable disease on a subsequent bone scan. Grade 2 hypertriglyceridemia persists at the time of this report, without specific treatment.

Dyslipidemia (all grades) is a common toxicity seen in up to 50% of breast cancer patients receiving everolimus [2], and is usually managed with either statins or fibrates.

In the present case, the introduction of fenofibrate resulted in a significant decrease of everolimus trough concentrations. Recent data have shown the impact of everolimus trough concentrations (used as a surrogate for its area under the concentration–time curve, as previously described [3]) on its efficacy and toxicity [5]. In this letter, we pinpoint that fenofibrate can decrease everolimus plasma concentrations, with potential clinically relevant consequences on its efficacy and toxicity. Even if no deleterious effect in terms of activity was seen in the present case, probably due to early discontinuation of fenofibrate, one would expect a lower activity of everolimus in patients receiving concomitantly fenofibrate, due to lower drug exposure [5].

Of note, no study to date has ever shown a significant impact of genetic variants in CYP3A4, CYP3A5 and MDR1, and a genetic predisposition can be reasonably ruled out in the present case.

According to the drug interaction probability scale (DIPS) [6], the drug–drug interaction between fenofibrate and everolimus was probable, with a DIPS score of 7.

Everolimus is approved for the treatment of advanced renal cancer, neuro-endocrine tumours and more recently in combination with exemestane in hormone-sensitive metastatic breast carcinoma, and is therefore increasingly prescribed. Clinicians should be aware of this potential drug–drug interaction involving fenofibrate, and should probably avoid treating everolimus-induced dyslipidemia with fenofibrate.

Whether other fibrates could avoid lowering everolimus plasma concentrations is uncertain. If fenofibrate is used in cancer patients receiving everolimus, our report suggests that trough plasma concentrations of everolimus should be monitored, with a goal of target of ≥10 ng/ml [5].

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disclosure

OM has acted as consultant for Astra-Zeneca, Roche, Bayer, Servier, Novartis, Pfizer and Glaxo-Smithkline.
MA has acted as a consultant for Novartis and Merrimack.
SD has acted as a consultant or speaker for Novartis, Roche, Glaxo-Smithkline, Amgen and Pfizer.
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references


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Reply to the letter to the editor ‘Measured and estimated glomerular filtration rate for carboplatin dose calculation’ by Cathomas et al.

In Annals of Oncology, Cathomas et al. [1] report the results of a retrospective study in a group of men (n = 426) treated with adjuvant carboplatin for stage I seminoma. The carboplatin dose was determined by the Calvert formula: (GFR + 25) × AUC, with a target area under the curve (AUC) of 7 mg ml/min. All patients underwent measurement of glomerular filtration rate (GFR) with radioisotope-based methods (131I-Cr-EDTA or 99mTc-DTPA). Measured GFR was compared with estimated GFR (eGFR) using various formulas, none of which carried out very well: if the carboplatin dose had been calculated using eGFR instead of actual GFR, a significant proportion of patients would have been under- or overdosed. The authors conclude that radioisotope methods are recommended when adjuvant carboplatin is prescribed for stage I seminoma, where doses below AUC 7 may be associated with inferior outcomes [2].

We previously published a smaller study (n = 68) [3] with the same design; it is encouraging that Cathomas et al. obtained similar results in their larger series, drawing the same conclusions. If the Cockroft-Gault [4], Jeliffe [5] or Wright [6] formulas, which are among the most popular choices in oncology for carboplatin dose calculation, had been used in our patients instead of measured GFR, 7.3, 95.6 and 7.3%, respectively, would have received a dose of carboplatin >10% lower than the correct one. The corresponding rates in the study by Cathomas et al. were 18, 63 and 24%. Overdosing is also a potential concern when using formulas: the proportion of patients in our study who would have received a carboplatin dose >10% higher than the correct one was 33.8% with the Cockroft-Gault formula, 1.5% with the Jeliffe formula and 35.3% with the Wright formula.