granulomatous reaction after chemotherapy and therapy with the checkpoint inhibitor ipilimumab [3–7]. These cases cannot be diagnosed as sarcoidosis as these are immune reactions related to immune regulation after chemotherapy and/or immunotherapy. Additionally, granulomatous reactions are not limited to the lung. As suggested by Berthod et al. [7], these reactions are immune-related adverse events. Perhaps, these reactions may be predictive for checkpoints inhibitors. At this point, appropriate terminology should be post-chemotherapy granulomatous reaction for cases treated with chemotherapy and post-immunotherapy granulomatous reaction in cases treated with immune checkpoint inhibitors or other immune therapies. We will see more similar cases in the near future due to the widespread use of checkpoint inhibitors. The correct terminology must be used by oncologists to avoid confusion for doctors dealing with sarcoidosis due to this chaotic terminology.

S. Paydas*
Department of Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
(*E-mail: sepay@cu.edu.tr)

disclosure
The author has declared no conflict of interest.

references
1. Cousin A, Toulmond M, Kind M et al. Pulmonary sarcoidosis induced by the anti-
2. Judson AM, Mongenthal AS, Baughman RP. Murray and Nadel’s textbook of
Respiratory Medicine, Chapter 66. 2015; 1188–1206.
3. Paydas S, Yavuz S, Disel U et al. Granulomatous reaction after chemotherapy for
4. Daly PA, O’Brien DS, Robinson I, Guckian M, Prichard JS. Hodgkin’s disease with a
granulomatous pulmonary presentation mimicking sarcoidosis. Thorax 1988; 43:
407–409.
5. Wilgenhof S, Mortion V, Seghers AC et al. Sarcoidosis in a patient with metastatic
melanoma sequentially treated with anti-CTLA-4 monoclonal antibody and selective
e7–e10.

doi: 10.1093/annonc/mdw193
Published online 3 May 2016

Benefit of therapeutic drug monitoring to disclose pharmacokinetic interaction between sunitinib and calcium channel blocker

Sunitinib is the standard first-line treatment for patients with metastatic renal cell carcinoma [1]. Cancer and aging coincide as causes of polypharmacy. The potential for pharmacokinetic drug–drug interactions is therefore large, as is the risk of adverse consequences. Sunitinib and SU12662 (active metabolite) are extensively metabolized by cytochrome P450 (CYP) 3A4. Additionally, sunitinib has a narrow therapeutic index. Therefore, patients treated with sunitinib are at substantial risk of having pharmacokinetic drug–drug interactions. Therapeutic drug monitoring (TDM) in patients treated with targeted therapies has been recently suggested to optimize the clinical management for particular situations including anticipated drug–drug interaction [2].

We describe the case of a 74-year-old male patient diagnosed with a 9-cm clear cell renal carcinoma, Fuhrman 4, treated by nephrectomy. Fourteen months later, brain metastases led to stereotactic radiotherapy. During follow-up, liver metastases were histologically proven. Since the patient exhibited an ECOG performance status 0, sunitinib was started at the recommended daily dose of 50 mg (4 weeks on/2 weeks off). His other medications included glibenclamide (2.5 mg thrice daily) and nicardipine (50 mg twice daily), which were continued at the same dose upon sunitinib initiation. At day 8, the patient experienced grade 2 hand-foot syndrome and his blood pressure was 160/80 mmHg. Although the pharmacokinetic steady state was not achieved, the plasma trough composite concentration (sunitinib 84 ng/ml + SU12662 82 ng/ml) was already supratherapeutic (composite target range: 50–100 ng/ml) (Figure 1) [2]. Given the potential inhibitory effect of nicardipine on CYP3A4 [3], nicardipine was switched to amiodipine 5 mg/day (CYP3A4 substrate). Sunitinib daily dose was maintained at 50 mg per day. Fourteen days later, blood pressure was normal and hand-foot syndrome had lowered to grade 1. Plasma trough composite concentration (sunitinib 56 ng/ml + SU12662 39 ng/ml) returned in the target range. After 2 weeks off treatment, no toxicity was noted during the second cycle. At day 70, trough plasma composite concentration (sunitinib 51 ng/ml and SU12662 33 ng/ml) remained in the target range and the computed tomography showed a partial response to treatment. To date (day 150),

![Figure 1. Evolution of plasma trough composite (sunitinib + SU12662) concentration (filled diamonds) and sunitinib/active metabolite SU12662 (filled squares) in a patient with metastatic renal carcinoma treated concomitantly with sunitinib and calcium channel blocker (nicardipine, then amiodipine). The patient was always treated with the recommended daily dose of sunitinib (50 mg once a day). At day 150, the patient is still under sunitinib 50 mg/day with partial tumor response and without any severe toxicity. The dashed lines represent the recommended target range for trough composite concentration (50–100 ng/ml) [2].](https://academic.oup.com/annonc/article-abstract/27/8/1651/1741256/Benefit-of-therapeutic-drug-monitoring-to-disclose)
the patient is still under sunitinib 50 mg/day with partial tumor response.

Sunitinib-induced hypertension is a very common toxicity in patients treated for renal cell carcinoma. The 1.7-fold decrease in plasma trough composite concentration after nicardipine discontinuation supports the hypothesis of significant inhibitory effect of nicardipine on both sunitinib and SU12662 CYP3A-mediated metabolism. This lower metabolic clearance of sunitinib and SU12662 resulting in a supratherapeutic composite concentration could lead to severe toxicity as previously reported [4]. However, the early use of TDM allowed managing the drug–drug interaction and preventing the onset of severe toxicities. We encourage clinicians to consider alternative antihypertensive options, such as angiotensin system inhibitors, which appear to have synergistic activity with sunitinib [5]. Overall, this case highlights the benefits in reviewing co-medication and measuring plasma drug concentration to individually adjust sunitinib treatment where necessary.

F. Da Silva¹,², A. Thomas-Schoemann³,⁴,⁵, O. Huillard¹,², F. Goldwasser¹,² & B. Blanchet³,⁴∗

¹Department of Medical Oncology, Cochin Hospital, AP-HP, Paris; ²Paris Descartes University, CARPEM, Paris; ³Department of Pharmacokinetics and Pharmacacochemistry, Cochin Hospital, AP-HP, Paris; ⁴Paris Descartes University, Paris; ⁵UMR8638 CNRS, Faculté de Pharmacie, Université Paris Descartes, PRES Sorbonne Paris Cité, Paris, France

∗E-mail: benoit.blanchet@aphp.fr

disclosure

The authors have declared no conflicts of interest.

references

doi: 10.1093/annonc/mdw182
Published online 26 April 2016

Reply to ‘Statistical controversies in clinical research: end points other than survival are vital for regulatory approval of anticancer agents’ by Saad and Buyse

In their recent article, Saad and Buyse address the drawbacks of using overall survival (OS) and progression-free survival (PFS) as surrogate end points for clinical benefit in prospective, randomized, cancer trials [1].

Given the diversity of patients and the consecutive treatments that they receive, there is an urgent need for more accurate end points, which specifically assess the benefit of the tested drug and which can be reached within a short timeframe.

However, while waiting for such end points, regulatory authorities still need to deal with OS and all kinds of response rate-derived end points (PFS, time to progression and overall response rate).

As we read in the article, the FDA granted approval for new drugs on response data only in 60% of cases in the period between 2003 and 2007. With regard to PFS, several cohort studies have, however, shown that the degree of interobserver agreement decreases with an increasing number of observers and that such disagreement can result in differently scored responses [2–6]. This is not just a matter of being familiar with the RECIST criteria. Choosing target lesions and strict follow-up of these lesions are variables, which can seriously harm the reliability of PFS data. Just imagine the very popular multicenter trial with 100 study sites and hundreds of radiologists (or other staff?), who have performed the response assessment. Quite often, such trials do not encompass a central response assessment review. And if a central response assessment review has taken place, the degree of concordance with the initial assessment and consecutive steps taken by the statistician are seldomly made clear in the study publication.

Study groups have come up with solutions aimed at improving the reliability of PFS as an end point variable, i.e. either by decreasing the number of observers who assess response or by using automated computed tomography volumetry [2–7].

Ideally, the oncological scientific societies should encourage pharmaceutical companies and researchers to implement either of these actions in future studies aimed at improving PFS.

H. K. van Halteren*

Department of Medical Oncology, Admiraal de Ruyter hospital, Goes, The Netherlands

∗E-mail: h.vanhalteren@adrz.nl

disclosure

The author has declared no conflict of interest.

references