Research letter

Paradoxical simultaneous regression and progression of lesions in a phase II study of everolimus in classic Kaposi sarcoma

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Dear Editor, The phosphatidylinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is activated in Kaposi sarcoma (KS) lesions in humans.[1,2] Sirolimus, an mTOR complex 1 (mTORC1) inhibitor, was effective in preclinical models of KS,[1] and is considered to be the standard of care post-transplantation in patients with KS.[2–4]

We aimed to investigate, in a phase II study, if everolimus, another mTORC1 inhibitor already approved in transplantation and oncology, would be a possible alternative treatment in classic or endemic KS. We hypothesized that 6 months of treatment with everolimus 10 mg daily would result in a clinical response, associated with a pharmacodynamic response in sequential tumour biopsies, in at least 50% of patients. Study design, evaluation criteria of response, pharmacodynamic studies and statistical methods are available online (see Supporting Information).

Between June and October 2008, 11 patients [median age 74 years (range 56–81)] were included in the study. The inclusion criteria are summarized in Table S1 (see Supporting Information). The median time since the diagnosis of KS was 3·7 years (range 0·9–20·0). Eastern Cooperative Oncology Group performance score was 0 in eight patients (82%) and 1 in two patients (18%). All patients had classic KS. Seven patients had received at least one line of systemic KS therapy (taxanes, liposomal anthracyclin, vinblastine, etoposide, bleomycin and/or interferon). The median time since the last KS therapy was 5 months. At baseline, seven patients had > 50 lesions, and eight patients had lymphoedema.

Interim analysis in April 2009 showed that eight patients (73%) had progressive disease (PD), two patients (18%) had stable disease (SD) and one patient (9%) had a partial response (PR). In the majority of cases, the classification of PD was due to the appearance of new lesions (Fig. 1). In all patients evaluated, there was stabilization in or a reduction in the size and palpability of the target lesions, with the exception of two patients who had increases of 15% and 22% in the target lesion size, respectively; however, this increase did not satisfy protocol conditions to be classified as PD.

In accordance with the protocol, the study was stopped after the interim analysis, as there was only one partial response. The treatment of eight patients out of the 11 was stopped owing to worsening of KS in two and toxicity (related or unrelated to the study) in the other six patients, and they were all withdrawn from the study before their 6-month evaluation. In the 6-month period following withdrawal of everolimus, certain lesions stopped progressing and other new lesions disappeared (Fig. S1; see Supporting Information). Given the unexpected rate of progression observed in the study, we suspected that treatment with everolimus had aggravated the disease.

The results obtained did not show any correlation between clinical response and whole blood everolimus concentrations (Fig. 2a). Whole blood trough everolimus concentrations

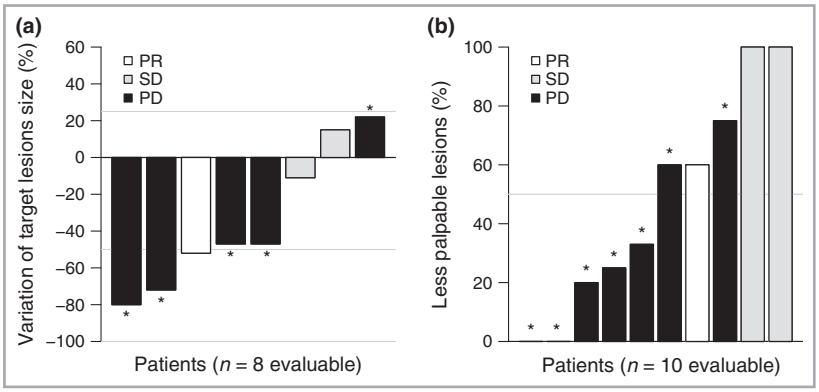

Fig 1. Disease progression was mainly due to the paradoxical appearance of new Kaposi sarcoma lesions. Waterfall charts showing, at study interruption, (a) the percentage change in target lesion size and (b) the percentage of less palpable lesions. The asterisks indicate the patients with new lesions. Despite overall reductions in target lesion sizes and reduction in palpability, disease progressed in the majority of patients according to the study's Aids Clinical Trial Group definition of progression. PR, partial response; SD, stable disease; PD, progressive disease.

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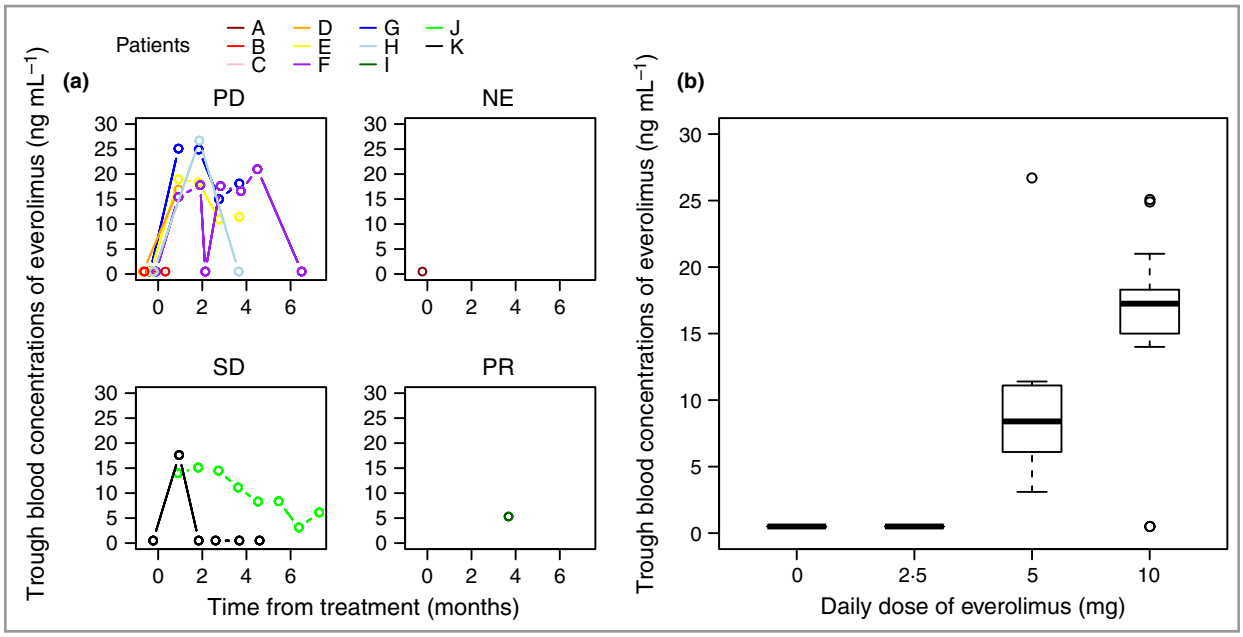

Fig 2. Trough blood concentrations of everolimus measured by high-performance liquid chromatography tandem mass spectroscopy. (a) Trough blood concentrations in individual patients according to clinical response over 6 months. (b) Trough blood concentrations according to daily dose. The box-and-whisker plots display the median, 25th and 75th percentiles of the distribution (the box), and the whiskers extend to the most extreme data point, which was no more than 1·5 times the interquartile range from the box. The levels obtained correspond to those observed in phase 1 oncology trials for the same dose levels. PD, progressive disease; NE, nonevaluable; SD, stable disease; PR, partial response.

increased with the dose received, and ranged from 0·5 ng mL^{-1} to 26·7 ng mL^{-1} (Fig. 2b). Among the patients who progressed, five remained on everolimus 10·0 mg daily and two received reduced doses of 5·0 mg daily; these patients may have had higher trough concentrations than stable patients, but the small sample size did not allow conclusions to be drawn. The five patients who progressed under everolimus and were treated for at least 1 month, had trough concentrations > 15·0 ng mL^{-1} between the first and second month.

Adverse events (AEs) thought to be related to the treatment are listed in Table S2 (see Supporting Information). Two serious AEs, which were not considered to be related to the treatment, occurred: one patient had severe anaemia, associated with gastrointestinal bleeding, due to a gastric cancer; the other patient had a fatal infectious lung disease, which occurred < 1 week after everolimus was started. Everolimus was stopped in one patient after an episode of atrial flutter, which occurred at 4 months and was considered potentially related to the treatment. Owing to toxicity, four patients (including the patient with a PR and one of the two patients with SD) received a reduced dose of everolimus of 5·0 mg daily, and the other patient with SD had the dose of everolimus reduced to 2·5 mg daily.

The median initial human herpesvirus (HHV)-8 viral load (expressed as $\log_{10}$ of $x + 1$) was 1·89 (range 0–4·34). The median highest viral load was 4·14 (range 0–6·6) (Fig. 3). Although the viral load increased during treatment, owing to the small number of responders no correlation could be made with disease progression.

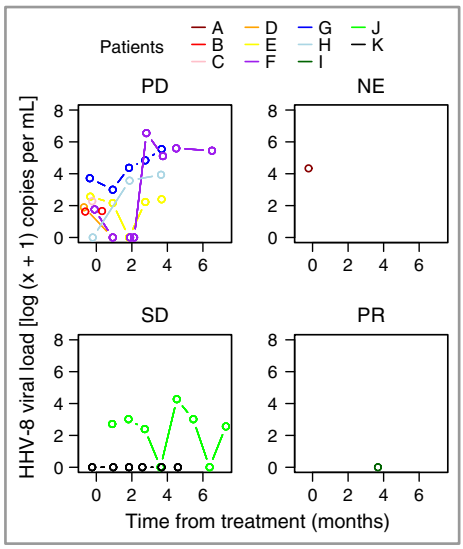

Fig 3. Individual human herpesvirus (HHV)-8 load during treatment showed an overall, but erratic, increase in load in patients who progressed. However, owing to the low number of responders, no correlation with progression could be seen. The load was measured retrospectively by quantitative real-time polymerase chain reaction analysis of *ORF26* using an ABI PRISM 7500 instrument (Applied Biosystems, Foster City, CA, U.S.A.). PD, progressive disease; NE, nonevaluable; SD, stable disease; PR, partial response.

Pharmacodynamic evaluation revealed that expression of *VEGF* isoforms [vascular endothelial growth factor (VEGF)121 and VEGF165] and of their receptor, *VEGFR2*, in sequential

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biopsies was either stable or increased in patients with PD, while it decreased in patients with SD (Fig. S2; see Supporting Information). The same trend was found for VEGF121 mRNA levels in blood (data not shown). Immunohistochemistry showed decreased expression of phospho-S6 kinase (a major direct target of mTOR), in all these patients (Fig. S3; see Supporting Information).

In five patients (two with SD and three with PD) there was a reduction in tumour density, an increase in oedema and in $CD8^+$ T-lymphocyte infiltration, and the appearance of or increase in B-lymphocyte infiltration. These results were not associated with disease status. With the exception of two patients, there was no relationship between reduction of tumour density (defined by the presence of CD31 tumour cells) and HHV-8 expression (defined by the presence of latency-associated nuclear antigen-positive cells) in the biopsies (Table S3; see Supporting Information). These results were confirmed by quantitative analysis of HHV-8 tumour load using quantitative real-time polymerase chain reaction (PCR) on the biopsies (data not shown).

It is unclear why there was regression in target lesions and yet a simultaneous development of new KS lesions elsewhere in the same patient. We believe that this paradoxical effect may have resulted from the interaction of two properties related to everolimus: an antitumoral effect on the one hand and an immunosuppressant effect on the other, with the latter enabling reactivation of HHV-8, as evidenced by the increase in viral load in blood. This increase in viral load is of particular interest, as in classic KS the viral load is generally low or undetectable.[5] An immunosuppressant effect may have been favoured by our initial choice of dose based on results from other phase I, I/II and II cancer clinical trials.[6,7] Although some recent data obtained in mice infected with lymphocytic choriomeningitis virus or macaques after vaccinia virus vaccination showed that mTORC1 inhibitors could improve antiviral memory $CD8^+$ T-cell responses,[8] in humans mTOR inhibitors are considered to be immunosuppressive agents and their use in patients with cancer has been shown to increase the risk of infection.[9] More specifically, studies on the use of everolimus in advanced hepatocellular carcinoma led to the flaring of hepatitis in 46% of patients seropositive for hepatitis B surface antigen with detectable serum hepatitis B virus DNA before treatment. The combination of very high everolimus drug levels and the reduced immune status of our elderly patients may explain these results.

Any conclusions that can be drawn from our study are restricted by the small sample size due to the interruption of the study. However, it provides useful insight into the behaviour of classic and endemic KS in a fairly elderly population not affected by other major pathologies or treatments treated with an mTORC1 inhibitor under clinical trial conditions. Further studies should evaluate inhibitors of the PI3K pathway using low dosages combined with an antiviral agent.[10–12]

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Clinical pictures of patients with (a, b) partial responses, (c–e) stable disease and (f) progressive disease. Photographs were taken before the initiation of everolimus treatment (baseline), after 3 months of everolimus treatment (M3) and, for the patient with progressive disease, 6 months after treatment withdrawal.

Fig S2. Pharmacodynamic effects of the tumour in treated patients. The lines show the individual evolution of the expression of the biomarkers [vascular endothelial growth factor (VEGF)121, VEGF165 and VEGFR2] at baseline (M0) and on treatment at 3 months (M3).

Fig S3. Expression of phospho-S6 kinase (shown in brown) by immunohistochemistry in the tumours of a selected patient who achieved a partial response (PR) at baseline and after 6 months of everolimus treatment. Sections counterstained with haematoxylin (magnification ×400).

Table S1. Inclusion criteria.

Table S2. Adverse events thought to be related to treatment, classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

Table S3. Immunohistological features of tumour biopsies.

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Conflicts of interest: none declared.

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Co-primary endpoints PASI 90 and IGA 0/1 at Week 16 were met.**Secondary endpoints. †N= mNRI, missing data were imputed with mNRI (patients with missing data following treatment discontinuation due to lack of efficacy or a TRAE were counted as non-responders; multiple imputation methodology was used for other missing data). ‡43.9% (n=189/431), and 43.4% (n=116/267) of biologic-naïve and TNFi-IR PsA patients achieved the primary endpoint of ACR 50 at Week 16 in BE OPTIMAL and BE COMPLETE, respectively (vs 10.0% [n=28/281] and 6.8% [n=9/133] placebo, p<0.0001); 54.5% (n=235/431) and 51.7% (n=138/267) maintained it at Week 52 (NRI).[4–6]

ACR 50, ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

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