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Philipp Kiewe, Eckhard Thiel

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Corresponding Author: Dr. Philipp Kiewe, M.D.

Corresponding Author's Institution: Charité Campus Benjamin Franklin

First Author: Philipp Kiewe, M.D.

Order of Authors: Philipp Kiewe, M.D.; Eckhard Thiel, M.D.

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Impressive response to temsirolimus in a patient with chemotherapy refractory diffuse large B-cell non-Hodgkin's lymphoma

Philipp Kiewe* and Eckhard Thiel

Dept. of Hematology, Oncology and Transfusion Medicine, Charité University Medicine, Campus Benjamin Franklin, Hindenburgdamm 30/31, 12200 Berlin, Germany

*Charité University Medicine, Campus Benjamin Franklin

Dept. of Hematology, Oncology and Transfusion Medicine

Hindenburgdamm 30

D-12200 Berlin, Germany

Tel.: +49-30-8445-2337

Fax: +49-30-8445-4468

Email: philipp.kiewe@charite.de

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Dear Editor,

Temsirolimus is a selective inhibitor of the cell proliferation promoting intracellular protein mTOR (mammalian target of rapamycin). Its activity in lymphatic malignancies has first been demonstrated in relapsed mantle-cell lymphoma [1]. Further studies confirmed activity in this lymphoma entity and established a weekly dosage of 75mg as approved treatment regimen [2], although a weekly dose of 25mg remains an effective treatment option [3]. Experience with temsirolimus in other entities of NHL is limited to a phase II study in recurrent DLCBL, follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma [4]. In 19 evaluable patients with DLCBL and a median of ≥ 2 prior treatment lines, a remarkable overall response rate of 42% was observed with a weekly temsirolimus dosage of only 25mg.

A 44-year old woman was diagnosed with diffuse-large B-cell Non-Hodgkin's lymphoma (NHL) limited to the tongue base (stage IBE) in June 2003. After initial treatment with 6 cycles of dose-intensified cyclophosphamide, adriamycin, vincristine, etoposide and prednisolone (Hi-CHOEP), a complete response was achieved. The patient relapsed in October 2006 with intrathoracic and abdominal manifestations. Salvage therapy included 3 cycles of rituximab, ifosfamide, carboplatin and etoposide (R-ICE) followed by high-dose carmustine, etoposide, cytarabine, melphalan (HD-BEAM) and autologous stem-cell transplantation resulting in complete response. In July 2008, second relapse occurred with cervical and abdominal lymph node enlargements. Treatment was initiated with 5 cycles of rituximab and bendamustine yielding another complete response. Remission, however, was short-lived, and in January 2009 disease recurred. Sequential treatment included one cycle of rituximab, dexamethasone, high-dose cytarabine, cisplatin (R-DHAP) and one cycle of

rituximab, high-dose cytarabine, mitoxantrone (dose-modified R-HAM) in reconfirmed CD20-positive disease followed by a second high-dose protocol with ^{90}Y-ibritumomab tiuxetan, cyclophosphamide, etoposide, carmustine (Z-CVB) and autologous stem-cell support. This time, only partial remission was achieved with disease progression shortly thereafter in August 2009. Further treatment lines including lenalidomide, two cycles each of gemcitabine/mitoxantrone and carboplatin/ifosfamide were ineffective.

In November 2009 the patient presented with a large intraabdominal tumor-bulk resulting in a massively distended abdomen. Lactate dehydrogenase (LDH) had risen to 480 U/L (< 247) and bone marrow function was poor with severe tricytopenia, predominantly thrombocytopenia of 50 x 10^9/l (150-400).

At this time, weekly monotherapy with 25mg temsirolimus was started. A dramatic clinical response was seen after only 5 infusions with normalization of the abdominal exam and LDH. No relevant toxicity was noted. The sixth temsirolimus infusion was combined with bendamustine after platelet counts had risen to 136 x 10^9/l. One week thereafter, restaging computed tomography (CT) scans confirmed clinical response with only minimal residual abdominal lymphoma manifestations compared with pre-treatment imaging (Fig 1a+b). Temsirolimus infusions were continued but unfortunately, tumor progression was observed four weeks later.

The very favourable response in our patient with highly pretreated refractory DLCBL, though short-lived, supports the evidence of a high activity of temisirolimus in NHL including DLCBL. Further investigations are clearly warranted, preferably in less advanced disease and in combination with chemotherapy. Moreover, the optimal dosage needs to be defined.

Figure 1 Abdominal CT scan without intravenous contrast-enhancement before temsirolimus treatment (a) and after six weekly infusions (b) showing only minimal residual lymphoma manifestations (arrow).

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Figure 1 a+b

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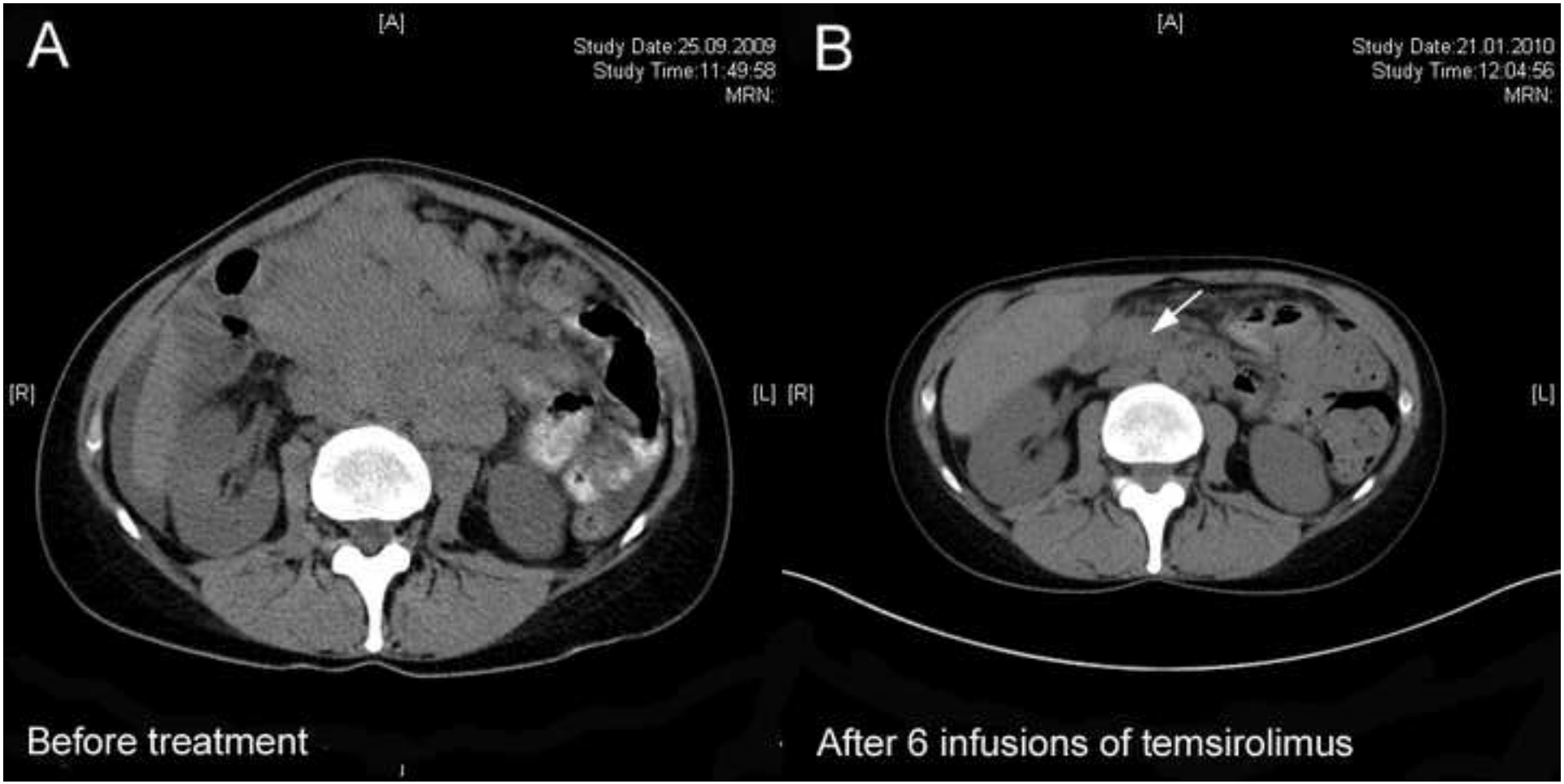

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