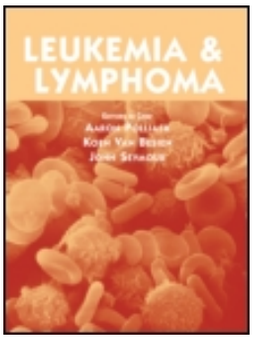

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

There is life in the old dog yet: thymidine kinase as predictive marker in diffuse large B-cell lymphoma

Clemens-Martin Wendtner

To cite this article: Clemens-Martin Wendtner (2013) There is life in the old dog yet: thymidine kinase as predictive marker in diffuse large B-cell lymphoma, Leukemia & Lymphoma, 54:11, 2343-2344, DOI: 10.3109/10428194.2013.807513

To link to this article: https://doi.org/10.3109/10428194.2013.807513

Leukemia & Lymphoma, November 2013; 54(11): 2343–2344

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.807513

informa
healthcare

COMMENTARY

There is life in the old dog yet: thymidine kinase as predictive marker in diffuse large B-cell lymphoma

Clemens-Martin Wendtner

Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine, Klinikum Schwabing, Academic Teaching Hospital of University of Munich, Munich, Germany

Thymidine kinase (TK) was initially described in the early 1950s as an enzyme being critically involved in the salvage pathway for DNA synthesis [1]. While the majority of TK activity that is detectable in serum is associated with the proliferative phase of the cell cycle (G1/S), another mitochondrial isoenzyme, TK2, is independent of the cell cycle. The role of serum TK as a prognostic factor in indolent lymphomas including chronic lymphocytic leukemia is well established, and has been extensively validated in several prospective clinical trials [2,3]. It has also been shown that high levels of TK are associated with advanced disease stage. In addition, TK can also be utilized as a predictive marker for survival, and high levels of TK before treatment were linked to inferior survival data in patients with newly diagnosed follicular lymphoma and peripheral T-cell lymphoma (PTCL) [4,5].

In this issue of ***Leukemia and Lymphoma***, Suzuki *et al.* evaluated the predictive power of TK in diffuse large B-cell lymphoma (DLBCL) [6]. The latter subtype of lymphoma has rarely been studied with respect to this particular parameter. Furthermore, this study exclusively included data obtained from treatment-naive patients homogeneously treated with the rituximab-containing regimen, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). This is indeed one of the few analyses that has evaluated an established marker such as TK in the rituximab era of chemoimmunotherapy. Here it is noteworthy that TK showed independent predictive value in a multivariate analysis that included other well-established prognostic markers such as age, performance status, revised International Prognostic Index (R-IPI), bulky mass and B symptoms. Since high TK activity correlated with inferior clinical response as well as inferior progression-free and overall survival after treatment with R-CHOP, the authors suggest that this is most likely to be due to a more malignant tumor phenotype present in a highly proliferative status (G1/S phase) of the lymphoma. This observation is of critical clinical importance, because alternative treatment strategies, including autologous or allogeneic transplant, should be considered in patients with high-risk DLBCL with high TK levels. Nevertheless, what to offer these high-risk patients still remains a challenge, since recent trials have been disappointing for young patients with high-risk DLBCL, at least in regard to high-dose chemotherapy followed by autologous stem cell transplant when compared to conventional chemotherapy (CHOEP-14) [7]. The role of allogeneic transplant has not yet been defined in patients with DLBCL who have a high risk for relapse, and ongoing trial activities have to be awaited [8]. In this respect, however, there are other new agents that hold promise to improve outcome for patients with DLBCL harboring a high-risk profile, including the spleen tyrosine kinase (Syk) inhibitor fostamatinib, the immune-modulatory drug lenalidomide, the proteasome inhibitor bortezomib, the Bruton's tyrosine kinase inhibitor (BTKI) ibrutinib, and others.

Nowadays it is generally accepted that DLBCL is a relatively heterogeneous lymphoma subtype with distinct features: gene expression profiling has revealed that DLBCL consists of at least three different molecular subentities, i.e. a germinal center B-cell like subtype (GCB), an activated B-cell like subtype (ABC) and a primary mediastinal B-cell lymphoma subtype (PMBL). Some biologic predictive factors such as MYC and BCL2 may be overexpressed in both the GCB and ABC subtypes, and strategies that target these complexes are currently being developed [9]. The question remains whether the predictive power of TK can also be validated for special histological subtypes of aggressive lymphomas such as Burkitt or double-hit lymphomas. Furthermore, it is still not clear whether the most recently defined specific molecular subtypes of DLBCL, such as the ABC subtype with its oncogenic MYD88 mutation, might be more prone to predictive analysis according to TK activity, since all of these analyses had not been performed at the time when data were collected for the present study by Suzuki and colleagues [6]. Furthermore, there are also new treatment strategies, beyond R-CHOP, commonly used, especially in these more aggressive types of lymphomas,

Correspondence: Clemens-Martin Wendtner, Dept. of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine, Klinikum Schwabing, Academic Teaching Hospital of University of Munich, Munich, Germany. E-mail: clemens.wendtner@uni-koeln.de

This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

that have not been evaluated in the retrospective study by Suzuki *et al*. reported here. These regimens include not only hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) in combination with methotrexate and cytarabine, but also the recently explored tyrosine kinase inhibitors such as the BTKI ibrutinib [10]. Ibrutinib and also drugs such as lenalidomide seem to be very active in the ABC subtype of DLBCL, potentially by augmenting interferon-β production and down-regulating transcription factors including IRF4 and SPIB [11]. Although we can still utilize some "old dogs" like TK in the context of prognostic parameters, the time has come to have a closer look at molecularly defined subgroups of DLBCL that will allow a more rational use of prognostic and predictive markers in the rapidly evolving era of targeted drugs for lymphoma treatment.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Reichard P, Estborn B. Utilization of deoxyribosides in the synthesis of polynucleotides. J Biol Chem 1951;188:839–846.
[2] Ellims PH, Eng Gan T, Medley G, et al. Prognostic relevance of thymidine kinase in adult non-Hodgkin's lymphoma. Blood 1981;58:926–930.
[3] Hallek M, Wanders L, Ostwald M, et al. Serum beta(2)-microglobulin and serum thymidine kinase are indepent predictors of progression-free survival in chronic lymphocytic leukemia and immunocytoma. Leuk Lymphoma 1996;22:439–447.
[4] Prochazka V, Faber E, Raida L, et al. High baseline serum thymidine kinase 1 level predicts unfavorable outcome in patients with follicular lymphoma. Leuk Lymphoma 2012;53:1306–1310.
[5] Suzuki K, Terui Y, Nakano K, et al. High thymidine kinase activity is a strong predictive factor for poor prognosis in peripheral T-cell lymphoma treated with cyclophosphamide, adriamycin, vincristine and prednisone. Leuk Lymphoma 2012;53:849–854.
[6] Suzuki K, Terui Y, Yokoyama M, et al. Prognostic value of high thymidine kinase activity in patients with previously untreated diffuse large B-cell lymphoma treated by rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone. Leuk Lymphoma 2013; 54:2412–2417.
[7] Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1). Lancet Oncol 2012;13:1250–1259.
[8] Papageorgiou SG, Cwynarski K, Kottaridis PD. The role of allogeneic haematopoietic progenitor cell transplantation in patients with diffuse large B-cell non-Hodgkin lymphomas (DLBCL). Bone Marrow Transplant 2013 Jan 14. [Epub ahead of print]
[9] Dunleavy K, Grant C, Wilson WH. Using biologic predictive factors to direct therapy of diffuse large B-cell lymphoma. Ther Adv Hematol 2013;4:42–57.
[10] Dasmahapatra G, Patel H, Dent P, et al. The Bruton tyrosine kinase (BTK) inhibitor PCI-32765 synergistically increases proteasome inhibitor activity in diffuse large-B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) cells sensitive or resistant to bortezomib. Br J Haematol 2013;161:43–56.
[11] Yang Y, Shaffer AL 3rd, Emre NC, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. Cancer Cell 2012:21:723–737.