The role of angiogenesis in non-Hodgkin lymphoma

Judit Mészáros Jørgensen, MD

The PhD dissertation was accepted by the Faculty of Health Sciences of the University Aarhus , and defended on September 30, 2005.

Official opponents: Niels Abildgaard, MD, Karsten Nielsen, MD, DMSci, and Cai Grau, MD, DMSci.

Tutors: Francesco d'Amore, MD, DMSci, professor Flemming Brandt Sørensen, MD, DMSci, Knud Bendix, MD, DMSci, and Johan Lanng Nielsen MD, DMSci.

Correspondence: Judit Mészáros Jørgensen, Grævlingevej 3, 8660 Skanderborg, Denmark. E-mail:rlg05juj@as.aaa.dk

Dan Med Bull 2005;52:254

ABSTRACT

The PhD study was performed during my appointment as clinical assistant at the Department of Haematology, Aarhus University Hospital, in the period 2001-2005.

The aims of the study were i) to evaluate the prognostic value of angiogenesis in the three most common subtypes of non-Hodgkin lymphoma (NHL): diffuse large B-cell (DLBCL), follicular (FL) and peripheral T-cell lymphoma (PTCL), using quantitative estimates of microvascular profiles, and ii) to assess the expression of angiogenic growth factors, VEGF and VEGF-C, and their receptors Flt-1, KDR and Flt-4.

The thesis consists of three parts:

1. A comparative investigation of different methods used to quantify microvascular profile density.
2. An estimation of the microvascular profile density by the microvascular density (MVD) and the Chalkley methods, and its correlation to histopathological parameters, clinical prognostic profiles and prognosis in 308 patients with NHL.
3. An assessment of the expression pattern of VEGF, VEGF-C and their receptors (Flt-1, KDR, Flt-4) at protein (immunohistochemistry) and mRNA level (in situ hybridisation) in the NHL subtypes.

Both the MVD and the Chalkley method showed that the lymphoma subtypes differed significantly in angiogenic scores. If measured within tumour areas, angiogenic scores were highest in PTCL, and lowest in FL. However, a remarkably high microvessel density was also found in the interfollicular areas of FL.

High interfollicular MVD scores correlated with a poor treatment response and survival in FL. FL cases with high Chalkley scores seemed to have a higher rate of histological transformation to DLBCL.

In PTCL, high MVD scores correlated with disseminated disease. However, in PTCL and DLBCL, the angiogenic scores had no impact on survival.

Expression of VEGF and VEGF-C and their receptors was found in all NHL subtypes, but variable expression patterns were observed. In general, cytoplasmic expression of angiogenic growth factors and receptors was more frequent in aggressive histologies. In FL, diffuse VEGF protein expression had an adverse effect on survival. In DLBCL, high VEGF-C and KDR expression correlated with treatment refractoriness, and high KDR expression also predicted a poorer survival. In PTCL, diffuse tissue distribution of VEGF mRNA correlated with a poorer outcome.

In general, growth factor expression correlated positively with the morphologically estimated angiogenic scores.

Our data suggest that angiogenesis and expression of VEGFs and their receptors in NHL may play a role in both the biological and clinical behaviour of NHL. Understanding the role of angiogenesis in NHL may improve our insight in the biology of this disease and lead to the recognition of new pathogenetic mechanisms, which is the prerequisite for the identification of new therapeutic strategies.