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COMMENTARY

Mantle cell lymphoma: curcumin nanodisks and possible new concepts on drug delivery for an incurable lymphoma

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Mantle cell lymphoma (MCL) generally has an aggressive course with a poor outcome and a median survival of 3–5 years [1]. More than a decade after the hallmark identification of the t(11;14)(q13;32) translocation in MCL, which is the underlying cause of the cell cycle dysregulation and overexpression of cyclin D1, the disease still remains basically incurable with standard combination chemotherapy [1]. About 15% of cases of MCL, however, have an indolent clinical course which can be treated more conservatively at diagnosis and generally have a better overall survival [2]. In principle, conventional chemotherapy is inadequate for the aggressive form of MCL, and although novel combinations based on more aggressive regimens such as Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), MAXI-CHOP (high-dose cyclophosphamide, doxorubicin, vincristine, and prednisone), and Ara-C (cytarabine) based regimens and others, combined with rituximab and subsequent transplant, have been introduced in recent years, long-term remissions and cure have still not been improved radically in MCL [1]. New phase III trials for newly diagnosed MCL are currently ongoing, and include novel approaches with combinations of bendamustine, proteasome inhibitors (bortezomib), and rituximab with lenalidomide and rituximab maintenance [3]. Since MCL is so difficult to cure with conventional and even more aggressive therapy, novel agents and new therapeutic approaches are legitimate and are indeed required for this incurable lymphoma subtype. In this respect, the article by Singh *et al*. in this issue of ***Leukemia and Lymphoma*** [4] dealing with the herb curcumin and nanodisk technology touches on a possible novel approach to MCL and is of interest for the future.

Curcumin (diferuloylmethane) is the active ingredient of the dietary spice turmeric (*Curcuma longa*) and an important spice in the Middle and Far East as well as India. Different groups have investigated its potential therapeutic benefit and efficacy in malignancies and have also shown its apoptotic effect [5]. It functions as a histone deacetylase inhibitor (HDAC) and could be regarded as a new member of this class of drugs already used in hematological malignancies [6]. Curcumin may also have a synergistic effect with green tea (*Camellia sinensis*), as described from studies in the Mayo Clinic in the USA against B-chronic lymphocytic leukemia (CLL) cells. This agent appears to suppress activation of nuclear factor κB [7,8], down-regulates Syc activity [9], and also has an effect on transcription factors, growth factors, and cytokines, which are all specific molecular targets [10]. Because altered apoptosis pathways exist in MCL and activation of Akt contributes to the pathogenesis and survival of MCL cells [11], it is indeed feasible that curcumin via its many effects on these and similar pathways as described in detail in this report by Singh *et al*. [4] may indeed prove to have potential and be effective in this disease and other lymphoproliferative disorders if utilized correctly and in optimal fashion.

The potential use and wider application of curcumin in hemato-oncological malignancies has been restricted by the fact that it is very insoluble and has poor bioavailability. In this respect the accomplished

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article by Singh *et al*. in this issue of ***Leukemia and Lymphoma*** is of great interest, as it contains some novel ideas and a proof of principle in relation to curcumin and its intracellular mechanism of action in MCL cell lines [4]. The authors report the development of a novel drug delivery system enriched for this herb, incorporating the bioactive polyphenol into nanodisks (nanovehicle) containing a disk-shaped phospholipid bilayer whose edge is stabilized by a scaffold protein recombinant human apolipoprotein. This method enhances its biological activity compared to free curcumin, and enables the delivery of an otherwise insoluble compound more effectively, causing increased growth arrest of the G1 phase of the cell cycle and decreased cyclin D1 levels within the cell. The data presented indicate that the curcumin nanodisks cause and induce apoptosis via reactive oxygen species (ROS) generation and activation of the caspase-3 pathway in cells of two MCL cell lines.

Further emerging new strategies aimed at targeting the existing biological pathways known to exist in MCL, which are linked with dysregulated control of cell cycle and impaired apoptotic pathways, are under way [12]. These include the use of immune modulators, proteosome inhibitors, and other promising agents, including the phosphatidylinositol 3-kinase inhibitor CAL 101, Bruton tyrosine kinase (BTK) inhibitors, and specific BiTEs (bispecific T-cell engagers), which may be introduced as part of the treatment algorithm [12]. More effective treatment still remains a major challenge in prospective studies for MCL. Individualized approaches will need to be followed and novel innovative programs will no doubt be welcomed in the future, particularly if individual molecular risk profiles of patients can be better defined as in other lymphoproliferative disorders.

The nanodisk technology, which deals essentially with hydrophobic drug delivery vehicles, has only been pioneered in recent years, and the group of investigators authoring this article in ***Leukemia and Lymphoma*** have developed these curcumin nanodisks and have recently reported on their formulation and characteristics [13]. In an earlier report in 2007 they also employed a similar technique for the delivery of all-*trans* retinoic acid (ATRA), thereby enhancing retinoic acid receptor mediated apoptosis and cell cycle arrest in MCL [14]. These results are encouraging in MCL cell lines and should now also be utilized on primary MCL cells isolated from human tumors and possibly in murine models of lymphoma, so as to show primary and *in vivo* cytotoxic effects.

All the above advances and new therapeutic regimens planned for MCL are exciting, but there still appears to be no ready solution for the individual patient seen in the daily clinic who is often outside of clinical trials. Furthermore, treating physicians will still be faced with the practical dilemma of how best to treat the individual case of MCL with a poor prognosis, when they are in fact left without a convincing curative regimen to offer such patients. In this respect the observations on curcumin and nanodisk delivery reported here [4] may provide a new avenue to explore in MCL biology and therapy. Perhaps the technology described for agents such as herbs and ATRA could also be utilized for more effective delivery of other drugs such as antibodies, and when utilized in an optimal manner could enhance standard chemo- and immunotherapy strategies for MCL and other tumors in the not too distant future.

At present, however, these are only experimental laboratory data from a study performed on two MCL cell lines, and do not provide clinical proof of principle of this technology. These are early days, and this concept and its translation into clinical practice still have a long road ahead.

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