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EDITORIAL

Systemic amyloidosis: are we moving ahead?

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ABSTRACT

Systemic amyloidoses are a wide group of diseases with different courses, treatments and prognoses. Unequivocal typing of amyloid deposits is important for correct diagnosis and appropriate treatment. At present, the most effective therapeutic approach is based on eliminating the supply of amyloidogenic precursor. New effective therapies will stem from our improved knowledge of the molecular mechanisms of amyloidosis.

Amyloidosis is a disease in which extracellular protein misfolding has a prominent role.[1] Localised or systemic deposition of protein fibrils with a β-sheet structure is the lowest common denominator of a wide group of diseases with different causes, courses, treatments and prognoses. The differential diagnosis of the various types may be beset with difficulties. In this issue, Hazenberg and colleagues propose a rationale step-by-step approach to the three major types of systemic amyloidoses.[2] These authors appropriately underline the paramount importance of correctly typing the amyloid deposits because this dictates both prognosis and treatment. Although genetic testing is necessary for an appropriate work-up of patients with amyloidosis,[3] unequivocal characterisation of amyloid deposits remains essential. Optical microscopy immunohistochemistry satisfactorily types reactive amyloidosis (AA) deposits, although it has several limitations in typing other amyloidoses. To overcome these difficulties, Arbustini *et al.* developed an electron microscopy immunohistochemistry method.[4] This method, which is feasible in major hospitals, unambiguously characterises amyloid deposits by demonstrating the typical ultrastructural features of the amyloid fibrils and, using specific antibodies, by co-localising the amyloidogenic protein with the fibrils.[5] Methods for extracting and chemically characterising the fibril proteins have been proposed,[6,7] but they require expertise and resources available in only a few centres worldwide. Treatment design also requires a high level of expertise. Currently, the most effective approach is the so-called 'precursor-product' concept, based on eliminating the supply of amyloidogenic precursor. This can sometimes be achieved easily, such as in colchicine treatment of most patients with familial Mediterranean fever. However, in amyloidosis caused by transthyretin variants, the optimal timing of liver transplantation and the possible need to co-transplant other organs, such as kidney and heart, irreversibly damaged by amyloid deposition, demand experience. The amyloidosis caused by monoclonal immunoglobulin light chains (AL) represents a difficult therapeutic challenge. It is necessary to achieve a fine balance between the need to annihilate the amyloidogenic plasma cell clone and the capacity of fragile amyloid patients to bear toxic chemotherapy. The chemotherapy approach was largely adapted from that used for multiple myeloma and includes high-dose melphalan followed by autologous stem cell rescue. It soon became clear that this produced intolerable treatment-related mortality and selection criteria were proposed.[8] This is also the case for less aggressive regimens such as VAD (vincristine, doxorubicin and dexamethasone). As reported by Van Gameren and colleagues in this issue, vincristine often has to be omitted because of peripheral and autonomic neuropathy, and doxorubicin because of its potential cardiac toxicity.[9] The dexamethasone scheduled in the

VAD regimen can also be too toxic for frail amyloid patients. We, therefore, developed a modified high-dose dexamethasone regimen which produced 35% responses in a median time of four months without significant toxicity.[10] Adding melphalan to the high-dose dexamethasone improved the response rate to 67% with 33% complete remissions without significant toxicity.[11] These results were achieved in patients who were ineligible for stem cell transplantation because of advanced organ involvement, making this regimen a viable alternative to autologous stem cell transplant. Van Gameren *et al.* also deal with the important issue of determining criteria for organ involvement and response to therapy.[9] Indeed, these criteria must be defined in order to facilitate comparison of populations of amyloid patients and effects of therapies. An ongoing international initiative to define such criteria should be finalised during the Xth Symposium on Amyloidosis in France in April 2004.

Better understanding of the molecular mechanisms of amyloidosis has led to new treatment approaches attacking different steps of the amyloidogenic cascade.[1] A few drugs aimed at mobilising amyloid deposits are under investigation. One of these, 4'-iodo-4'deoxydoxorubicin,[12] developed by our group, awaits better definition of its schedule and possible integration into a comprehensive therapy approach to amyloid disease. The pivotal mechanism underlying cellular damage caused by the amyloid process is being intensively investigated. Its clarification will have a strong impact on redirecting the search for new drugs. We are moving ahead: improved care of this complicated disease will be achieved by dismantling the amyloidogenic process through the integrated use of several drugs presently under development.[13] This will put the emphasis on early diagnosis, to be able to treat these patients before the amyloid process has irreversibly damaged organ function. The protean clinical presentation of amyloidosis requires a high level of alertness by physicians. While differential diagnosis and treatment necessitate the expertise of specialised centres, timely identification of these patients depends on education, which requires appropriately funded concerted initiatives.

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