AL Amyloidosis:
A Comprehensive Update from Fundamentals to Emerging Therapies

Efstathios Kastritis
National and Kapodistrian University of Athens, Greece

AL amyloidosis is characterized by a low-level expansion of an indolent, small plasma or B-cell clone that produces amyloidogenic light chains. Amyloid aggregates or preceding intermediaries cause direct cell damage through their proteotoxicity, and amyloid deposits distort tissue architecture, and, eventually, lead to organ impairment. AL amyloidosis is a rare but underdiagnosed disease, with a diverse clinical presentation which depends on the organ tropism of the amyloid fibrils. Cardiac and renal involvement is most common, but any organ can be affected, resulting in complex and both specific and non-specific phenotypes. To diagnose the disease a high degree of suspicion is required. Raising awareness is critical, identifying those at high r risk may be beneficial and a systematic approach using newly emerging screening biomarkers may help achieve early diagnosis, which remains an unmet need. The diagnostic approach but also the management should be multidisciplinary. Supportive care tailored to the management of organ dysfunction is paramount to survival and minimization of treatment-associated toxicity. In terms of specific therapy, the initial therapeutic goal is to rapidly eliminate the clonal plasma cell that produces the circulating amyloid precursor and achieve a complete hematologic response with minimal toxicity. Treatment is tailored to the initial risk assessment of the patients. Treatments are based on regimens adapted from the expanding options that are available for multiple myeloma patients and hematological response rates have improved. Currently daratumumab-bortezomib combinations have shown to improve complete hematologic response rates, organ response rates and overall survival. Although not formally proposed, achieving undetectable minimal residual disease as assessed by next-generation methods, or undetectable circulating toxic light chains with sensitive mass- spectrometry may lead to improved long term outcomes. Important, organ response rates are strongly associated with deeper hematologic response but usually lag behind hematological response and are also dependent on the initial organ function reserve. Emerging options further change the management of patients who fail to achieve rapidly a deep hematologic response, including mainly BCL-2 targeting drugs (for patients harboring t(11;14) and BCMA targeting therapies (ADCs, bispecific, CAR-Ts). Monoclonal antibodies directed against the amyloid deposits have been explored to aid amyloid clearance and improve organ function, but data are still negative, although some progress was recently made, suggesting that specificity of this drugs remains a critical component for their efficacy.