NEW CHALLENGES IN CLL IN 2010

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CLL is the most frequent leukemia in the Western hemisphere, while it is rare in other geographic areas, e.g. Japan. In view of the progressive extension of life expectancy, the prevalence of CLL is increasing. Over 70% of patients are greater than 65 years at diagnosis and frequently present comorbidities. For decades it has been known that CLL is a highly heterogeneous disease. The possibility of identifying biologic features associated with a different clinical outcome is modifying our approach to CLL. An extended biologic approach can enable a precise differential diagnosis between CLL and other B-cell chronic lymphoproliferative disorders and identify parameters associated with a different prognostic likelihood. This is important in light of the broad therapeutic armamentarium today available for CLL. We no longer can rely only Chlorambucil, but also on purine analogs, monoclonal antibodies, the broadening use of chemo-immunotherapy, stem cell transplant procedures and a spectrum of new compounds. It is today realistic to consider for patients with CLL an algorithm of treatment (or non-treatment) based not only on clinico-hematologic considerations, but also on biologic parameters.

We are facing new challenges in CLL today. Among these: 1) a biologically-based prognostic stratification; 2) a different approach for younger patients with poor prognostic markers; 3) the concept of disease eradication; 4) a change in the definition of remission; 5) monitoring of minimal residual disease; 6) CLL in the 'elderly'; 7) the role of consolidation and maintenance; 8) the significance and clinical impact of monoclonal B-cell lymphocytosis (MBL).
Chronic lymphocytic leukemia (CLL) can truly be chronic, but the clinical course of CLL patients is heterogeneous, with some patients experiencing rapid disease progression requiring aggressive and sometimes repeated therapies. Most recently, the heterogeneity can be obtained more accurately through the use of validated clinical risk models and the use of novel (B-cell related) prognostic features. Thus, features in the clinical risk models are relatively easy to obtain and include age, Rai stage, sex, absolute lymphocyte count, beta-2 microglobulin and number of lymph node regions. These parameters have been found to be independently associated with patient survival. Importantly, they have now been validated in two independent series with the ability to predict time to treatment and overall survival (OS) even when applied exclusively to Rai stage 0 patients. The novel biologic prognostic factors, truly reflective of leukemic B-cell biology, include ZAP-70, immunoglobulin heavy chain (IGHV) gene mutation status, and cytogenetic abnormalities on fluorescent in situ hybridization (FISH) testing. These have been found to be robust predictors of treatment-free survival and OS even among newly diagnosed patients. These prognostic tools play an important role in the current counseling and management of CLL patients. Prognostic assays can also be integrated into risk stratification systems and used to predict responses to our current treatment approaches. In this discussion, we will review the available tools to stratify patient risk and emphasize how they can be used in clinical practice to individualize patient counseling, guide the frequency of follow-up, and inform treatment selection.
CLL TREATMENT: CURRENT STATUS AND FUTURE VENUES

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Treatment of patients with chronic lymphocytic leukemia (CLL) has experienced important progress in the last decade. As a result of recently randomized trials the combination of fludarabine, cyclophosphamide, and rituximab (FCR) is now considered the treatment of choice for both previously untreated and treated patients with CLL. Importantly, there is some indication that in patients with no prior therapy FCR results not only in a significantly longer progression-free survival but also a longer overall survival. In spite of this progress, there is still a lot of room for improvement and many questions waiting answer. For example, (1) there is an important proportion of patients in which due to comorbidity or advanced age FCR can not be safely given; (2) patients with 17p deletions or mutations do not respond to FCR; and (3) CLL continues being incurable. Several new monoclonal antibodies (MoAbs) and antileukemic agents are ready for prime time use in CLL therapy and hopefully should improve current treatment results. Among new MoAbs, Ofatumumab and GA-101 are new anti-CD20 agents that have already demonstrated good clinical activity. In addition, new treatment agents targeting not only leukemic cells but also microenvironment are of interest. In that regard, lenalidomide is an immunomodulatory agent widely investigated in many hematologic malignancies, including CLL, with positive results. Different phase II and phase III trials investigating these agents in combination are underway. Other areas which deserve investigation are the role of maintenance therapy in CLL, as well as the use of minimal residual disease (MRD), an important surrogate for prolonged survival, as treatment end-point. Finally, since patients failing modern chemoimmunotherapy have very poor outcome, more effective “salvage” therapies are urgently needed and safer allotransplantation procedures required.
FROM BENCH TO BEDSIDE AND BACK: IDENTIFICATION OF NOVEL RHAMM-DERIVED EPITOPE AS PROMISING TARGET FOR IMMUNOTHERAPY OF CHRONIC LYMPHOCYTIC LEUKEMIA

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The receptor for hyaluronic acid mediated motility (RHAMM) is leukemia associated antigen (LAA) in chronic lymphocytic leukemia (CLL). In recent peptide vaccination clinical trial with dominant RHAMM-derived epitope regulatory T cells (Treg) were induced in 66% vaccinated CLL patients. While the tolerance is limited to dominant epitopes we aimed to identify a cryptic epitopes that might circumvent tolerance mechanisms and in order to increase affinity modified them heteroclitically.

We screened in silico 50 peptides with different heteroclitical modifications using SYFPEITHI algorithm and calculate affinity to MHC-I complex. Further, we choose 10 peptide pairs (cryptic - modified) which affinity increased to the highest extent and screened them in vitro assay for the affinity. In functional studies we screened 5 peptide pairs by ELISPOT analysis using CD8+ T cells isolated from peripheral blood (PB) of CLL patients and healthy donors. We found that CD8+ cells from CLL patients presensitized with peptides: R9Y (YLQLDAFEV); R13YL (YLQGSLDV); R15Y (YLKTLDEL); R17YL (YLQELNKL) as well as R19YL (YLKHVVKL) specifically recognized T2 cells pulsed with respective peptides with the highest frequency for R9Y (90%). In chromium-51 release assays, R9Y-primed CD8+ T cells from CLL patients were able to effectively lyse R9Y-peptide pulsed T2 cells as well as CLL leukemic cells. In addition, mAb-based MHC I blockade demonstrated that the observed peptide-specific lysis was MHC I-restricted.

In conclusion, we defined a novel RHAMM-derived CD8+ restricted, heteroclitical, cryptic epitope R9Y which might represent an interesting target for immunotherapy of CLL.