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New paradigms in the anti-CD20 treatment of lymphoid malignancies

Chair: M.J. Keating (Houston, USA)

The biology of B-cell CD20 antigen and its potential as a therapeutic target

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Risk-stratified approach to treatment for patients with CLL

M.J. Keating (Houston, USA)

THE BIOLOGY OF B-CELL CD20 ANTIGEN AND ITS POTENTIAL AS A THERAPEUTIC TARGET

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The CD20 antigen is a transmembrane protein that is expressed on the majority of mature B-cells, but not on stem cells, plasma cells, or non-B-lineage cells within the body. Although the function of CD20 is not fully understood, there is evidence to support a role in the regulation of the cell cycle and apoptosis. CD20 is found on over 90% of B-cell lymphomas and other lymphoid tumors of B-cell origin. It is an ideal target for monoclonal antibodies because it is expressed at high levels on most B-cell malignancies but is not shed from the plasma membrane and does not become internalised following antibody binding. This allows the anti-CD20 monoclonal antibody to bind to its target on the cell surface for extended periods and deliver a sustained immunological attack. These favourable characteristics have led to anti-CD20 monoclonal antibodies being developed for immunotherapy of various B-cell malignancies. A number of biological effects of anti-CD20 antibodies may contribute to their anti-tumour activity in vivo. These include antibody-dependent cell-mediated cytotoxicity (ADCC), complement-mediated cytotoxicity (CMC), and induction of apoptosis/anti-proliferation. Rituximab, an IgGκ chimeric (human/mouse) monoclonal anti-CD20 antibody, was the first monoclonal antibody to be approved for the treatment of cancer patients. There is strong evidence to suggest that ADCC mediated by cytotoxic lymphocytes, monocyte/macrophages and possibly neutrophils may be the principal mechanism-of-action of rituximab. The success of rituximab has led to the development of a number of new antibodies, several of which have genetically altered sequences that result in greater binding affinity to the FCγR3a on ADCC effector cells, whereas other novel anti-CD20 antibodies have a higher affinity for killing by CMC and/or have a ''tighter'' binding to the CD20 target. The safety and efficacy of these newer antibodies is currently being explored in clinical trials.

FOLLICULAR LYMPHOMA: OVERCOMING RITUXIMAB RESISTANCE

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In 1997, rituximab became the first anti-CD20 monoclonal antibody to be approved for the treatment of a malignancy. Since then, treatment with rituximab has resulted in significant responses in patients with most subtypes of B-cell lymphoma. Follicular non-Hodgkin's lymphoma (NHL) has proven to be the most sensitive of the lymphoma subtypes to rituximab, with overall response rates of 80% and 60% in untreated and previously treated patients, respectively. Moreover, therapeutic strategies using rituximab in combination with systemic chemotherapy have been found to result in higher response rates and improved survival compared with rituximab or chemotherapy alone. Approximately 40% of patients with relapsed/refractory CD20+ follicular NHL do not respond to treatment with rituximab as a single agent and 40% of patients who respond to first treatment with rituximab will not benefit from subsequent retreatment. The precise nature of rituximab unresponsiveness is poorly understood but the proposed mechanisms may be broadly divided into two groups: tumour-related factors, such as downregulation of targeted extracellular CD20 antigen or acquisition of a protective phenotype (by upregulation of complement inhibitory proteins etc) and host-related factors, such as Fcγ receptor polymorphisms. Therapeutic approaches that may be able to overcome rituximab resistance include biological combination immunotherapy, radioimmunoconjugates and engineered antibodies. A number of next-generation anti-CD20 monoclonal antibodies, engineered to display higher affinity than rituximab for FcγR3a and/or lower immunogenicity than rituximab, are currently undergoing pre-clinical and clinical evaluation. One of these, ofatumumab, is a fully human IgG1κ monoclonal antibody that binds to a novel CD20 epitope. In vitro studies have shown that ofatumumab is able to induce effective killing of rituximab-resistant tumour cells expressing low levels of CD20 and high levels of complement inhibitory proteins. Ofatumumab may be overcoming rituximab resistance because it binds to the target for a significantly longer period of time than rituximab. Ofatumumab is currently being evaluated in patients with follicular NHL that are refractory to rituximab in combination with chemotherapy or rituximab maintenance therapy.

THE NEXT GENERATION OF ANTIBODY THERAPIES FOR NHL

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Rituximab, a chimeric (human/mouse) anti-CD20 monoclonal antibody changed the paradigm for treatment of patients with B-cell lymphoma. When used as a single agent, rituximab has consistently provided clinical responses in approximately 30-50% of previously treated patients and it also improves the efficacy of chemotherapy regimens in various forms of non-Hodgkin's lymphoma (NHL). However, a substantial proportion of patients with NHL fail to respond to rituximab and others will ultimately develop rituximab-resistant disease.
Directly radiolabeled anti-CD20 monoclonal antibodies produce greater single-agent efficacy response rates than rituximab in patients with transformed and follicular NHL

but they are associated with significant haematological toxicity. These haematological issues preclude treatment of some patients and limit ability to combine these agents concurrently with chemotherapy.

Many new immunologically-based therapies for the treatment of patients with follicular NHL are currently being developed, including the next generation anti-CD20 monoclonal antibodies. Some agents that have completed early clinical trials include: veltuzumab, a humanized (90-95% human) anti-CD20 antibody; ocrelizumab, a humanized version of murine 2H7 antibody and ofatumumab, a fully human IgG1κ monoclonal antibody that binds to a different epitope of CD20 than rituximab. Other genetically enhanced anti-CD20 antibodies are just entering early clinical trials, e.g. AME-133, PRO131921, GA-101.

In addition, novel monoclonal antibodies targeting other cell-surface antigens are also being investigated, either as single agents or in combination with rituximab. These include the anti-CD80 antibody galiximab, the anti-CD40 antibodies SGN-40 and HCD122 (CHIR-12.12) and the anti-CD22 antibodies, epratuzumab and inotuzumab. While considerable challenges exist in their development, the use of monoclonal antibodies and other forms of immunotherapy, such as vaccines and allogeneic transplantation, offers considerable potential to improve outcomes for patients with NHL.

THERAPEUTIC IMPLICATIONS OF THE BIOLOGICAL PROFILE OF CLL

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Chronic lymphocytic leukaemia (CLL) is the most frequent type of leukaemia in the Western world and is characterised by a highly variable clinical course. Over the recent years innovative and highly effective therapeutic approaches such as targeted therapy, antibody-chemotherapy and stem cell transplantation have been developed. Modern treatments can induce remission rates of over 90% in first-line therapy and may result in survival time of approximately 10 years. However, some patients are primary refractory or develop treatment resistance during the course of the disease, a situation with a particularly poor prognosis and median survival times in the range of only one year. Therefore, there is a pressing need for novel therapeutic approaches. In recent years, there has also been dramatic progress in our understanding of molecular pathogenesis and outcome prediction in CLL. Genetic parameters such as genomic aberrations (e.g. 11q-, 17p-), the mutation status of the variable segment of immunoglobulin heavy chain genes (VH), "surrogate markers" (e.g. CD38, ZAP-70, LPL, etc.), and serum parameters (ß2-MG, TK, sCD23) provide prognostic (in relation to survival) and predictive (in relation to treatment response) information for individual patients independently of clinical disease characteristics such as stage. Particularly, some markers have been associated with rapid disease progression (i.e. +12, 11q-, 17p-, unmutated VH, ZAP-70, CD38, ß2-MG, TK), resistance to treatment (i.e. 17p-), short remission duration (i.e. 11q-, 17p-, unmutated VH, ß-2MG), and short overall survival (i.e. 11q-, 17p-, unmutated VH, ZAP-70). Currently, these molecular markers are about to enter the stage of risk stratification for the treatment of individual patients.

RISK-STRATIFIED APPROACH TO TREATMENT FOR PATIENTS WITH CLL

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Over the past decade, considerable advances have been made in the treatment of patients with chronic lymphocytic leukaemia (CLL). While for many years alkylating agents were considered the drugs of choice for first-line treatment of progressive and symptomatic CLL, more recent treatment approaches include the use of purine nucleoside analogues, such as fludarabine, together with monoclonal antibodies – most commonly the anti-CD20 antibody rituximab but also the anti-CD52 antibody alemtuzumab. Overall response rates as high as 95% have been reported in clinical trials of chemoimmunotherapy. However, all patients eventually relapse and there is a need for new, effective, well-tolerated therapies. A novel therapy that is currently undergoing clinical trials for the treatment of CLL is ofatumumab, a fully human anti-CD20 monoclonal antibody. Positive early (phase I/II) clinical study results have shown that ofatumumab induces rapid responses in patients with relapsed CLL and is well tolerated. A phase III study is currently ongoing in patients with CLL who are refractory to fludarabine and alemtuzumab or fludarabine refractory patients for whom treatment with alemtuzumab is inappropriate due to the presence of bulky tumour in the lymph nodes. The clinical course of CLL is known to be highly variable, with survival ranging from months to decades. This clinical heterogeneity poses critical questions concerning the identification of patients with high risk, early stage disease who are likely to be suitable candidates for novel therapies that could alter the natural course of their disease. A number of molecular and cellular markers have been identified that can predict response to treatments and survival in patients with CLL. The incorporation of these prognostic markers into the design of future clinical trials and the use of rigorous pretreatment evaluation protocols (including disease staging and assessment of a patient's overall fitness/performance status) should enable primary and second-line treatment decisions to be made with greater confidence.