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Chair: M. Ghielmini (Bellinzona, CH)

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MABTHERA-BASED THERAPY FOR DLBCL: INCREASING THE PATIENT'S CHANCE OF CURE

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Combination chemotherapy with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone over a 21-day cycle; CHOP-21) became the established treatment in the 1970s for diffuse large cell lymphomas, which included diffuse large B-cell lymphomas (DLBCL). Attempts at dose intensification in the next two decades were largely unsuccessful, although more recent studies suggested there may be a benefit from dose intensification, particularly by shortening the period between cycles, e.g. CHOP-14.[1] Rituximab, when used alone for resistant or relapsed DLBCL had modest activity, but when given as initial therapy in combination with CHOP-21 it resulted in a highly significant improvement in complete response rate and overall survival.[2] The benefits were highly cost effective. The seminal trial was in elderly patients, but subsequent studies in younger patients confirmed the value of R-CHOP-21 as initial therapy. Rituximab is also efficacious when combined with the accelerated CHOP-14 regimen, and it is not clear whether in the post-rituximab era CHOP-14 remains superior to CHOP-21. This is being addressed in several large, randomised trials. The results from randomised trials have been confirmed in several population-based studies. Addition of rituximab to conventional dose salvage regimens also increases the response rate in relapsed patients, which is essential to enable transplantation strategies.[3]

The dose and scheduling of rituximab has been largely pragmatic and studies of higher rituximab does are underway. Initial studies of rituximab maintenance therapy have indicated little value after R-CHOP induction,[4] but further studies are in progress. Having established the principle of immunochemotherapy, other antibodies will now be evaluated. More efficacious anti-CD20 antibodies are being tested as, in the setting of DLBCL, greater B-cell depletion would be acceptable. Many antibodies to other antigens are also available to be given either with or instead of rituximab. Other ongoing studies address the role of antibodies conjugated either to toxins or radioisotopes.

One of the difficulties in improving the overall outcome in DLBCL is that those patients who do relapse may be more resistant to re-induction. Novel strategies for these patients may be required.

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CHARTING 10 YEARS OF PROGRESS: ARE WE CLOSER TO CURE IN FL?

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Defining cure in cancer is not an easy task. Patients with aggressive tumours are cured if they do not relapse within a few years of remission, while patients with indolent cancers can relapse 15 or 20 years after the first remission and are therefore more difficult to define as cured.

In indolent lymphoma, including follicular lymphoma (FL), the efficacy of treatment must first be judged on surrogate end points such as event-free survival (EFS) or duration of clinical or molecular remission. Therapeutic efficacy, as judged by surrogate end points, has sometimes corresponded to a prolonged survival and higher proportion of patients cured. However, in some cases, such as high-dose chemotherapy for first-line FL, this has not occurred: two studies showed that significantly prolonged EFS did not translate into prolonged overall survival (OS).[1,2] There are, however, plans for studies underway to challenge this finding by including rituximab in induction and maintenance therapy, and randomising autologous stem cell transplantation (ASCT), with the goal of achieving long-term remissions and potentially cure in these patients.

In FL, the only treatment to have shown some hints of cure (i.e. plateau of the survival curve lasting over 10 years) is allogeneic transplantation. Nevertheless, this modality has not become standard treatment because of its excessive toxicity.

Another encouraging modality is the addition of rituximab to chemotherapy, which was recently shown to substantially improve patient survival both in single randomised trials and, even more pronounced, in a meta-analysis of all the randomised clinical trials performed to date.[3] This observation is further substantiated by historical comparisons between cohorts treated before and after the rituximab era, with a trend towards improved survival as the decades go on.[4]

Besides adding rituximab to chemotherapy, maintaining remission with regular rituximab infusions has also been shown to significantly prolong EFS, and a trend towards an improvement of OS was recently demonstrated by a meta-analysis of all the randomised clinical trials of rituximab maintenance therapy.[5]

A notable exception to this is the Eastern Cooperative Oncology Group (ECOG) trial of rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP), followed by rituximab maintenance therapy or observation. In this study, rituximab maintenance therapy had a significant impact on progression-free survival, but with follow-up to date no significant difference in OS has been described between the two treatment arms.[6] Possible explanations for this may include the relatively small number of patients randomised or the fact that the induction chemotherapy was extremely effective and it could therefore have left behind few tumour cells on which the rituximab maintenance therapy could have acted. Still, even with very effective treatments, all patients eventually relapse, showing that in the treatment of FL we are

still facing a small population of clones which are both chemotherapy and rituximab resistant. These clones are finally responsible for patients' death, either due to tumour overgrowth or transformation into diffuse large B-cell histology.
Even though today the survival prognosis of patients with FL has improved, the chance of curing these patients will probably rely on the discovery of new drugs and new treatment modalities.

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INDUCTION AND MAINTENANCE THERAPY FOR FL: MY CLINICAL PRACTICE

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Background: Follicular lymphoma (FL), the most common single type of lymphoma seen in North America, presents unique challenges in its management: (1) with a median age at presentation of 65 years, most patients are elderly; (2) 90% of patients harbour advanced-stage disease, requiring systemic intervention; (3) although a minority of asymptomatic patients do not require initial intervention, more than 80% of patients require treatment within 4–5 years; (4) although the median survival now exceeds 7–8 years, 10–20% of patients die in the first 2 years and most patients eventually succumb to lymphoma, not other conditions; (5) transformation to more aggressive diffuse large B-cell lymphoma occurs in 3% of patients every year and often proves rapidly fatal. There is a clear need for effective interventions.
Recent advances: In the past decade, several seminal observations about FL have been made: (1) the addition of rituximab to primary chemotherapy improves both progression-free survival (PFS) and overall survival (OS); (2) the addition of rituximab to second-line chemotherapy improves PFS and OS; (3) rituximab maintenance therapy improves PFS and OS when added to second-line immunochemotherapy and probably when added to primary immunochemotherapy; (4) rituximab can be given safely by rapid infusion, sparing treatment resources; (5) the addition of rituximab substantially improves treatment outcomes for transformed lymphoma. At the British Columbia Cancer Agency (BCCA) we have built our primary and secondary treatment regimens on these observations.
Current BCCA approach: Previously untreated patients with symptomatic FL are treated with cyclophosphamide, vincristine, prednisolone and rituximab (R-CVP). Those with responsive disease (> 90%) also receive rituximab maintenance therapy (375 mg/m^2 iv over 90 mins every 3 months for 2 years). Transformed lymphoma is treated with R-CVP plus doxorubicin (R-CHOP) followed by rituximab maintenance therapy. This approach reserves doxorubicin until it is crucially necessary, for transformed lymphoma, and maximises the impact of immunotherapy with rituximab while minimising the overall impact on resources (maintenance therapy with a total of only eight cycles of rituximab; rapid infusion for convenient outpatient treatment).
Conclusion: Recent advances in the treatment of FL enable clinicians to treat this disease effectively, conveniently and with a substantial positive effect on progression-free and overall survival while minimising inconvenience and resource impact.

TRANSFORMING THE OUTLOOK FOR CLL PATIENTS

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Although treatment paradigms for chronic lymphocytic leukaemia (CLL) have evolved over the past few decades, new developments have had a limited impact on patient outcomes: no improvement in patient survival has yet been described in a randomised clinical trial comparing any two treatment interventions in CLL. For this reason, the primary goal of treatment for many patients, particularly those with advanced (stage III–IV) disease has often been symptom relief. New agents now being developed have the potential to transform the way we approach treatment of this chronic disease, allowing us to change the primary goal of treatment from symptom relief to extending remission and, ultimately, even survival.
The outcomes of CLL therapy are strongly dependent on a number of patient factors, including age, disease stage and the presence or absence of chromosomal abnormalities or single gene mutations.[1–3] Disease stage is the most significant factor in determining the optimal treatment approach, and current guidelines recommend first-line treatment with systemic chemotherapy or immunochemotherapy for all patients with advanced disease.[4] Until recently, fludarabine-based chemotherapy was the treatment of choice for previously untreated or relapsed disease, with the addition of cyclophosphamide with or without mitoxantrone (FC or FCM) offering improved response rates and progression-free survival, particularly in younger patients.[5–9]
Despite the improved outcomes with FC and FCM, less toxic monotherapies are often preferred for elderly patients (aged >65 years), with a primary treatment goal of symptom relief, and there is still a need for new options to increase response rates, remission duration and survival across all patient groups.
Several Phase II clinical studies have now shown that adding rituximab to conventional chemotherapy produces the highest response rates ever seen in CLL. In previously untreated patients, an overall response rate (ORR) of 90% has been demonstrated with rituximab plus fludarabine (R-F), with 47% of patients achieving a complete response (CR).[10] Adding cyclophosphamide to this regimen (R-FC) leads to an ORR of 95%, with 72% CRs,[11] while R-FCM shows an equally high ORR of 97%, with 80% of patients achieving a CR, of whom 69% are minimal residual disease-negative.[12]
Encouragingly, improvements in overall survival (OS) are seen with rituximab-based therapies when compared with historical controls treated without rituximab. A historical comparison showed that R-F significantly improves OS compared with fludarabine alone (probability of 2-year OS: 0.93 vs 0.81, respectively, $p = 0.003$).[13] Similarly, R-FC improves OS compared with historical controls treated with F±M/C ($p = 0.001$).[14] Rituximab-based therapies also allow improved responses in relapsed CLL, and treatment combinations including R-FC and R-FCM have again showed promising responses in this setting.[15,16] Rituximab maintenance therapy may also help increase the quality and duration of response.[17,18]
In the light of these positive Phase II data, R-FC induction is now being assessed in large, randomised Phase III trials in both first-line and relapsed settings, and the results of the CLL-8 and REACH trials will tell us whether rituximab-based therapy will transform the outlook for CLL patients. It is noteworthy that interim analysis of CLL-8 has now demonstrated that the addition of rituximab improved progression-free survival by greater than 35% and therefore the study achieved its primary objective.

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LOOKING TO THE FUTURE OF LYMPHOMA THERAPY

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The outlook for patients with non-Hodgkin lymphoma, in particular diffuse large B-cell lymphoma (DLBCL), has improved dramatically during the rituximab era, with significant improvements in survival and an increased chance of cure.[1,2] Seven-year follow-up of the pivotal Groupe d'Etudes des Lymphomes de l'Adulte (GELA) trial of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) compared with CHOP chemotherapy alone has now confirmed that this survival benefit is durable.[3] Here, we will look to the future of lymphoma therapy with a focus on DLBCL, and ask which new developments over the next 7 years may potentially lead to further improvements in patient survival.
In the immediate future, improvements are most likely to come from refinements of the current "standard" combination of R-CHOP, such as scheduling optimization,[4] infusional drug delivery,[5]the substitution of "next generation" anti-CD20 antibodies or the addition of other currently available biological agents such as bevacizumab (RA-CHOP).[6] Outcomes from salvage may be enhanced by the addition of rituximab to high-dose chemotherapy.[7,8] Next-generation anti-CD20 antibodies under development include ocrelizumab,[9] veltuzumab,[10] ofatumumab[11] and GA101, a humanised antibody that demonstrates increased antibody-dependent cellular cytotoxicity compared with rituximab.[12,13]
Over the longer term, we are looking to new molecular targets for the development of novel therapies. New monoclonal antibodies are being developed to target alternative cell surface antigens, and these may prove to be effective combination partners for rituximab. For example, the anti-CD40 ligand antibody SGN-40 has shown some activity in preliminary studies in relapsed DLBCL, follicular lymphoma and mantle cell lymphoma.[14] An anti-CD80 antibody (galiximab) is also under development. Other biological agents under development include temsorilimus, an inhibitor of the mTOR serine/threonine kinase, which is known to drive cell cycle progression in many human cancers.[15] This agent is currently in Phase II development in relapsed/refractory DLBCL and a variety of other lymphoma types.[16] One pathway that is being targeted by multiple new therapies is the death receptor (DR) 4 and 5 pathway. A recombinant, soluble form of Apo2 ligand (Apo2L), also known as tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), has been developed that activates cell surface DR4

and DR5 to induce apoptosis,[17] and is being studied in combination with rituximab for the treatment of follicular lymphoma. Similarly, the monoclonal antibodies mapatumumab (anti-DR4), apomab (anti-DR5) and lexatumumab (anti-DR5) have potential anti-tumour activity by targeting this pathway. An alternative and equally promising class of drugs are the BH3 mimetics, such as ABT-737, which induce apoptosis in cells showing cellular damage or stress and therefore may be active in lymphoma.[18] Finally, B-lymphocyte stimulator receptor 3 (BR3) and its ligand B-lymphocyte activating factor (BAFF) are both potential targets of monoclonal antibody therapy for lymphoma.

Although these novel agents are all still in early clinical development, each has potential anti-lymphoma activity, and may help further build on the substantially improved survival achieved during the rituximab era.

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