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 who did 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 can only 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 towards an improvement of OS was recently demonstrated by a meta-analysis of all the randomised clinical trials.\(^3\) 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.\(^4\) 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 may be required. 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.\(^5\)

References

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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.

References

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 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 progresses 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 further 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 immunotherapy and probably when added to primary immunotherapy; (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 (35 mg/m2 given every 2 months for 1 year). Transformed lymphoma is treated with R-CVP plus doxorubicin (R-CHOP) followed by rituximab maintenance therapy. This approach reserves doxorubicin until it is critically necessary, for transformed lymphoma, and maximises the impact of immunotherapy with rituximab, minimising its impact on resource (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 leukemia (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 from symptom relief to extending the potential to transform the way we approach treatment of this chronic disease, III–IV) disease has often been symptom relief. New agents now being developed have the promise to improve the outcomes of CLL therapy are strongly dependent on a number of patient factors, allowing us to change the primary goal of treatment from symptom relief to extending the quality and duration of response.1,2

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).3,4 Adding cyclophosphamide to this regimen (R-Fc) leads to an ORR of 95%, with 72% CRs,5 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.6,7 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 improved OS compared with fludarabine alone (probability of 2-year OS: 0.93 vs 0.81, respectively, p = 0.003).8

Similarly, R-FC improves OS compared with historical controls treated with FAMC (p = 0.001).9 Rituximab-based therapies also allow improved responses in relapsed CLL, and treatment combinations including R-FC and R-FCHP have again showed promising responses in this setting.10,11 Rituximab maintenance therapy may also help increase the quality and duration of response.12,13

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.

References

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.1–3 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.2 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 infusion 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).6,7 Outcomes from salvage may be enhanced by the addition of rituximab to high-dose chemotherapy.5,8 Next-generation anti-CD20 antibodies under development include cedrelumab,9 veltuzumab,10 obatuzumab11 and GA101, a humanised antibody that demonstrates increased antibody-dependent cellular cytotoxicity compared with rituximab.5,12

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-CD30 ligand antibody SN-40 has shown some activity in preliminary studies in relapsed DLBCL, follicular lymphoma and mantle cell lymphoma.12 An anti-CD30 antibody (galiximab) is also under development. Other biological agents under development include tenosilimus, an inhibitor of the mTOR serine/threonine kinase, which is known to drive cell cycle progression in many human cancers.13 This agent is currently in Phase II development in relapsed/refractory DLBCL and a variety of other lymphoma types.14 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

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and DR5 to induce apoptosis, 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. 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.

References