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New approaches to indolent lymphoma - Section 2

Update on follicular lymphoma: Time beyond chemotherapy?

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Take-home messages

- Immunochemotherapy is still the standard of care in frontline and first relapse.
- Efficacy, toxicity, quality-of-life and costs of new approaches have to be compared in long-term follow-up with existing regimens.
- There is a clear need for identification of predictive markers enabling individually tailoring of treatment regimens for subgroups of patients.

With the introduction of CHOP chemotherapy in 1976 this regimen has become a worldwide accepted standard in the treatment of non-Hodgkin's lymphoma. A big jump in the outcome was achieved when the CD20 antibody rituximab entered to the marked in the nineties. Nowadays, using immunochemotherapy the overall survival in patients with advanced follicular lymphoma (FL) is getting close to 20 years. However, most patients relapse within 5 to 7 years, and about 20% of patients' experience progression of disease within 2 years. Especially this group of patients has a poor outcome.[1] In 2013, Rummel *et al*. published their landmark paper showing that reducing the intensity of chemotherapy does not consequently results in a loss of efficacy.[2] In a randomized non-inferiority trial the authors compared bendamustine/rituximab (BR) with R-CHOP in patients with newly diagnosed stage III and IV indolent lymphoma. It was clearly shown the BR was well tolerated and prolongs progression-free survival (PFS) compared to R-CHOP. Based on these results, BR is used by most investigators as first-line chemotherapy in FL.

With the expanding knowledge of the biology and pathogenesis of B cell malignancies, several new compounds acting through a variety of mechanisms have been investigated in clinical trials. In contrast to cytostatic agents, these agents are characterized by a specific target on the surface of the lymphoma cell, in the intracellular pathway or in the microenvironment of the lymphoma cell (an overview is given in Table 1). But why to change an effective, well-known chemotherapeutic regimen? In general, a chemotherapy-free approach has to demonstrate to be more active and less toxic compared to standard therapies. Ideally, new approaches should offer innovative options for high-risk patients with early relapse, they should have the potential to overcome disease resistance that develops over time, they should avoid cumulative toxicities from successive therapies, they should reduce the risk of transformation and they should raise a chance of cure.

Targeting the cell surface

In recent years, the search for CD20 antibodies with improved activity compared to rituximab has been of particular interest. Ofatumumab is an anti CD20 agent which may have an increased complement dependent cytotoxicity. However, its role in FL is still unclear since there is no significant improvement in rituximab-refractory patients.[3] Obinutuzumab is another CD20 antibody which is claimed to have a higher antibody-dependent cellular cytotoxicity and more effective apoptosis induction compared to rituximab. In combination with chemotherapy, obinutuzumab achieve a significant better PFS in first-line compared to a rituximab-containing regimen.[4] In rituximab-refractory patients, the combination of obinutuzumab and bendamustine documented an effective treatment with a deep level of remission and was recently approved by the authorities.[5] However, in a head to head comparison with rituximab in rituximab pretreated patients, obinutuzumab failed to show a survival benefit.[6]

A variety of further monoclonal antibodies, antibody drug conjugates and bispecific antibodies (which also interact with the microenvironment) are under evaluation in FL (Table 1). Most of them show activity but it is still unclear what will be their definitive role.

Intracellular targets

At this time, idelalisib is the only compound which already received approval as monotherapy in Europe for relapsed/refractory FL. It is an orally available inhibitor of the

New approaches to indolent lymphoma - Section 2

delta isoform of phosphatidylinositol 3-kinase (PI3K) targeting key signaling molecules downstream of the B cell receptor. Approval based on results from a pivotal phase II study by Gopal *et al*.[7] In this study, 125 heavily pretreated patients (FL: 72 patients) received idelalisib until progression or intolerance. Patients achieved a median PFS of 11.0 months and a median OS of 20.3 months. It was also shown that idelalisib may have significant clinical activity in high-risk and doubly-refractive FL following early relapse.[8] However, because of an excess of atypical infections, the safety of idelalisib is still under discussion. Duvelisib is an inhibitor of the gamma and delta isoform of PI3K, showing a median PFS of 8.4 months and a median OS of 18.4 months in a phase II study in patients refractory to rituximab.[9] However, 63% of patients had dose modifications due to adverse events and 17% of patients discontinued treatment.Bruton Tyrosine Kinase (BTK) is a molecule which is crucial for function and survival of the B cell receptor. Ibrutinib is a first-in-class, selective, and irreversible inhibitor of the BTK and already plays an important role in the treatment of CLL, mantle cell lymphoma, and M. Waldenström. In FL, several trials evaluate its activity as a single agent and as part of a combination regimen. In a phase II trial of ibrutinib and rituximab, the overall response rate (ORR) in 60 patients with untreated FL was 85% with a rate of complete remission (CR) of 35%.[10] Ibrutinib was discontinued in 15% of patients due to adverse events. In immunochemotherapy-refractory FL, ibrutinib achieved an ORR of 20.9% (10.9% CR), and a median duration of response of 19.4 months.[11] Serious adverse events were reported in 48.2% of patients.

Venetoclax is a highly selective orally available inhibitor of BCL2, which is typically overexpressed in FL. In 29 pretreated patients with FL, the ORR was 38% (14% CR) with a median PFS of 11 months.[12]

Table 1. Selected targeted drugs in follicular lymphoma.

Targeting the cell surface	
Target	**Agent**
CD20 (type I antibody)	Rituximab*, Ofatumumab, Ocrelizumab, Ublituximab, Veltuzumab
CD20 (type II antibody)	Obinutuzumab*
CD22	Epratuzumab, Inotuzumab Ozogamicin°
CD79b	Polatuzumab Vedotin°
CD19	Coltuximab Ravtansine°
CD37	Otlertuzumab
CD80	Galiximab
HLA-DR	IMMU-114
CD3/CD19	Blinatumomab
Intracellular targets	
Target	**Agent**
PI3K	Idelalisib* (PI3Kδ), Duvelisib (PI3Kδγ), Copanlisib (PI3Kαδ)
BTK	Ibrutinib, Acalabrutinib
BCL-2	Venetoclax
Syk	Entospletinib, Fostamatinib
HDAC	Vorinostat
Proteasome	Bortezomib, Carfilzomib
MTOR	Temsirolimus, Everolimus
MDM2	Idasanutlin
EZH2	Tazemetostat
Targeting the microenvironment	
Target	**Agent**
'Immunomodulation'	Lenalidomide
PD-1	Nivolumab, Pembrolizumab, Pidilizumab
PD-L1	Atezolizumab, Durvalumab
KIR	Lirilumab
CD137	Urelumab

**EMA-approved in follicular lymphoma; °antibody drug conjugates.*

New approaches to indolent lymphoma - Section 2

Targeting the microenvironment

The interaction between lymphoma cells and the microenvironment plays a critical role in the pathogenesis of FL. Immunotherapeutic agents and checkpoint inhibitors have the potential to enhance the immunocompetence directed against the lymphoma cell.

Lenalidomide has only limited activity as single agent in relapsed FL, but efficacy is greatly enhanced in the combination with rituximab. In frontline, this combination achieved a CR rate of 87% with a PFS (3 years) of 78.5%.[13] The most common grade III/IV toxicity was neutropenia in 35% of patients. The results of the phase III Relevance trial comparing rituximab/lenalidomide with rituximab/chemotherapy are expected soon.

To date, several trials with so called checkpoint inhibitors are ongoing. The combination of pidilizumab, a presumed PD1 inhibitor, with rituximab in relapsed FL shows a ORR of 66% (CR 52%).[14] The regimen was well tolerated.

Are we now ready to abandon chemotherapy in FL? There is no doubt that non-cytotoxic agents are active in FL. There is also no doubt that these agents have side effects and the combination of new drugs may result in unacceptable toxicity.[15,16] When considering a chemotherapy-free approach in FL, it is important to keep in mind that:

- immunochemotherapy is still the standard of care in front-line and first relapse;
- efficacy, toxicity, quality-of-life and costs of new approaches have to be compared in long-term follow-up with existing regimens;
- there is a clear need for identification of predictive markers enabling individually tailoring of treatment regimens for subgroups of patients.

It is really exiting to move away from standard immunochemotherapy and to move in the era of targeted therapies, but the target patient has not been defined yet.

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