Management of autoimmune complications in patients with lymphoid cancer

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Abstract:
Autoimmune conditions can occur at any temporary relationship with malignant lymphomas. In many instances, treatment at diagnosis is not required, but symptomatic autoimmune conditions represent an indication for treatment particularly in chronic lymphoproliferative diseases. Treatment is selected depending on the predominant condition - autoimmune disease (immunosuppression) or lymphoma (anti-lymphoma therapy). Steroids as well as anti-CD20 antibodies are effective against both and may suppress the autoimmune complication for a prolonged period. Efficacy of B-cell receptor inhibitors has provided us with novel insights into the pathophysiology of antibody-producing B-cells. Screening for underlying autoimmune conditions is part of the lymphoma work-up since other drugs like immunomodulators or checkpoint inhibitors should be avoided or used with caution. Here we discuss diagnostic challenges and treatment approaches for different situations involving lymphomas and autoimmune cytopenias.

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Management of autoimmune cytopenias in patients with lymphoid cancer

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KEY POINT SUMMARIES:

- Autoimmune complications may require immunosuppressive or anti-lymphoma treatment depending on clinical needs
- Steroids, anti-CD20 antibodies as well as novel agents are effective not only against the lymphoma, but frequently against B cells producing autoantibodies

KEY WORDS: Lymphoma, autoimmune disease, autoimmune cytopenias, treatment indications
ABSTRACT

Autoimmune conditions can occur at any temporary relationship with malignant lymphomas. In many instances, treatment at diagnosis is not required, but symptomatic autoimmune conditions represent an indication for treatment particularly in chronic lymphoproliferative diseases. Treatment is selected depending on the predominant condition - autoimmune disease (immunosuppression) or lymphoma (anti-lymphoma therapy). Steroids as well as anti-CD20 antibodies are effective against both and may suppress the autoimmune complication for a prolonged period. Efficacy of B-cell receptor inhibitors has provided us with novel insights into the pathophysiology of antibody-producing B-cells. Screening for underlying autoimmune conditions is part of the lymphoma work-up since other drugs like immunomodulators or checkpoint inhibitors should be avoided or used with caution. Here we discuss diagnostic challenges and treatment approaches for different situations involving lymphomas and autoimmune cytopenias.
Introduction and Background

The association between lymphoid neoplasms and autoimmune diseases has long been noted. Definitive evidence linking the diseases in terms of causality is rare. However, there is compelling evidence for their co-occurrence.\(^1\)\(^2\) Autoimmune diseases occur with a prevalence of approximately 10% in lymphoid neoplasms.\(^3\) However, this varies between entities with a high prevalence in certain lymphomas (from 7.4% in Hodgkin’s lymphoma to 18% in marginal zone lymphoma).\(^4\)\(^5\) The majority of autoimmune conditions (AIC) is associated with B cell lymphomas and much less frequent with T cell non-Hodgkin lymphomas (NHL).

Autoimmune complications in lymphoproliferative diseases frequently affect the hemopoietic system, but may have rheumatologic, endocrinologic, neurologic or other manifestations.\(^6\) In this article we will focus on the management of autoimmune cytopenias illustrated by practical cases.

Autoimmune cytopenias can occur at any time during the course of lymphoproliferative diseases: (1) before lymphoma diagnosis, (2) at diagnosis of lymphoma and (3) after diagnosis or treatment of lymphoma.\(^7\) In some cases, the autoimmune phenomenon may even be related to anti-lymphoma therapy.\(^7\)\(^8\) The pathophysiology of autoimmune cytopenias in relation to the time of occurrence as well as to their association with predisposing diseases (e.g. rheumatic diseases) or treatments may be very different.

Among autoimmune cytopenias autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are the most frequent, but other conditions such as immune mediated neutropenia or pure red cell aplasia do occur. The diagnosis of autoimmune cytopenias is usually made using the criteria of the respective diseases. In some cases antibodies are detected without symptomatic disease. B-cell mediated (antibody-dependent) AICs are predominant, but T cells may also play an important role.\(^4\) The antibodies involved may be monoclonal (e.g. IgM kappa in cold agglutinin disease) or polyclonal (e.g. warm antibodies in WAIHA).

Clinical management consists in appropriate diagnostic work-up, but the most important decision to make is whether treatment is needed and if so, should it be directed against the AIC, against the lymphoma or against both. Here we describe a number of typical scenarios with practical solutions and recommendations.
Autoimmune hemolytic anemia

Autoimmune hemolytic anemia (AIHA) may either occur shortly before lymphoma diagnosis or be detected during lymphoma workup. AIHA is best characterized in chronic lymphocytic leukemia (CLL), but is found as a complication in many lymphoma entities as well as in solid tumors.\(^{10-17}\) Severe AIHA may lead to initiation of anti-lymphoma treatment, but in many cases immunosuppression is able to stabilize the condition for further watchful waiting (Figure 1A-C). IWCLL Guidelines for instance explicitly state that autoimmune conditions mimicking a CLL Binet C stage can be treated with immunosuppressive therapy.\(^{18}\) A direct antiglobulin test (DAT) is part of the CLL screening program and is positive in up to 14% at diagnosis.\(^{11,18}\) Reticulocytes are elevated and biochemical signs of hemolysis such as elevated bilirubin and LDH are usually present. Other features pointing to AIHA are morphologic abnormalities of the blood smear (polychromasia and spherocytosis). The prevalence of AIHA in CLL is approximately 2.9% in stable Binet stage A disease compared with 10.5% in stage B and C.\(^{19}\) Clinically, a discrepancy between a normal platelet count and anemia with high reticulocytes should lead to the suspicion of AIHA. The anti-red cell autoantibody involved in CLL is predominantly of IgG warm type, but cold agglutinins of IgM type have been observed.\(^{20}\) If the diagnosis of warm AIHA is established and the hemoglobin is below 10 g/dL or the patient is symptomatic, prednisone at a dose of 1 mg/kg is usually effective and should be continued according to AIHA treatment recommendations (Table 1).\(^{21,22,23}\) Rituximab (R)( 4 times weekly at 375 mg/m\(^2\)) is recommended in case of steroid failure. Rituximab response are high (71%) but are not always long lasting.\(^{12,24}\) Due to its anti-lymphoma activity it can also be used in first line, e.g. in case of contraindications for steroids. Rituximab is also the treatment of choice if cold agglutinins are present (Table 1).\(^{21}\)

**Patient 1**

A 67year old man with a typical CLL in experienced a sudden drop in hemoglobin from 12.9 g/dL to 9.3 g/dL with an increase in reticulocytes to 163 \(\times 10^9/L\), MCV 110fL, while platelets were still normal. Haptoglobin was reduced (<25 mg/dL) with slightly elevated indirect bilirubin and LDH. The DAT was positive for anti-IgG1 but not complement C3d consistent with warm AIHA (wAIHA). Standard treatment with prednisolone at 1 mg/kg body weight was initiated. The anemia responded within 1 months (Hb 11.0 g/dL, reticulocytes 74 \(\times 10^9/L\)), prednisolone was slowly tapered and hemoglobin was back to 13.5 g/dL in September 2012, when steroids were stopped. The DAT was still positive, which is a common finding. However, 4 months later, the AIHA re-occurred with a hemoglobin of 8.7 g/dL.
The patient was now treated with 4 weekly doses of rituximab 375 mg/m² and had a complete response of his wAIHA with a remaining DAT positivity for IgG. Eighteen months later, the CLL had progressed to Binet C with thrombocytopenia without signs of immune thrombocytopenia in blood or bone marrow, but again accompanied by AIHA. Bone marrow biopsy showed heavy infiltration with CLL and reduced number of megakaryocytes. The patient was treated with 6 cycles of rituximab and bendamustine (absence of TP53 abnormalities, IgHV status mutated) and hematological CR as well as a complete response of AIHA were achieved. The patients is now 78 years old in ongoing CR. This case shows the spectrum of treatment options ranging from immunosuppression to anti-lymphoma treatment.

**Treatment of AIHA and/or lymphoma with chemoimmunotherapy or novel agents**

**Warm autoimmune hemolytic anemia.** Patients experiencing progression of their underlying lymphoma (in this case CLL) may be better treated with chemoimmunotherapy (Figure 1A). Regimens containing anti-CD20-antibodies are effective against both, the AIC and the lymphoma. However, fludarabine (particularly without rituximab) should be avoided due to its potential to cause AIHA by itself.²⁵⁻²⁷ R-bendamustine has shown excellent activity with response rates of 81% for AIHA and 77% for CLL (Table 1).²⁸ This outweighs the few cases of complicating AIHA after bendamustine therapy.²⁹ Rituximab, cyclophosphamide and dexamethasone (RCD) is another good choice, particularly in CLL or indolent lymphomas.³⁰,³¹ Some patients may even convert to Coomb’s negativity. The treatment is effective for other autoimmune cytopenias in CLL. A combination of rituximab with cyclophosphamide, vincristine and prednisone has also been used.³² In contrast to primary warm AIHA, splenectomy is not a major option in lymphoma-associated AIHA due to an increased risk of infection.³³ The Bruton’s tyrosine kinase inhibitor ibrutinib is the preferred option in patients not responding to chemoimmunotherapy or those with TP53 abnormalities. Ibrutinib induces long-term responses in AIHA and CLL.³⁴⁻³⁸ A low rate of treatment-emergent autoimmune conditions has been reported.³⁹ The Bcl-2 inhibitor venetoclax seems to be effective against AIHA as well, although few cases have been published so far.⁴⁰,⁴¹ Novel anti-CD20 antibodies such as ofatumumab or obinutuzumab should have at least similar activity as rituximab, but published data are rare.⁴² CLL guidelines now recommend use of BTK or Bcl2 inhibitors in most cases. The low rate of autoimmune complications associated with these therapies is outweighed by the anti-lymphoma effect. With large data sets still missing, we prefer sequential therapy or simultaneous administration of an
anti-CD20 antibody in patients with AIHA in need of anti-lymphoma therapy with ibrutinib or venetoclax.\textsuperscript{23}

The following case describes treatment of a CLL patient with a del(17p) with ibrutinib accompanied by an unusual complication.

**Patient 2**

A 35-year old female patient was diagnosed with CLL with a TP53 mutation and deletion (17p). WBC was 93 x10\(^9\)/L with a platelet count of 239 x10\(^9\)/L and a severe anemia with a hemoglobin of 6.5 g/dL. Low haptoglobin as well as elevated LDH and total bilirubin were noted, but the DAT was negative (as in 5\% of AIHA cases).\textsuperscript{21} Interestingly, the patient had very low reticulocyte counts (0.007 x10\(^12\)/L, normal values 0.027-0.116 x10\(^12\)/L). Bone marrow examination revealed typical CLL but suppressed erythropoiesis. A diagnosis of anemia due to CLL indicating a Binet stage C or CLL with pure red cell aplasia (PRCA) (based on low reticulocyte counts and diminished erythropoiesis in the bone marrow) with DAT negative AIHA was made. The patient was dependent on blood transfusions. CLL-specific with ibrutinib was initiated resulting in normalization of white blood cells but without hemoglobin response (6 g/dL). We reasoned that the AIC was predominant in this case. Therefore, ibrutinib was stopped and the patient was treated prednisone at 1 mg/kg followed by 4 weekly doses of rituximab. The hemoglobin increased to normal levels (14.9 mg/dL) Ibrutinib was reinitiated and the patient is still in complete response of CLL and PRCA.

This case shows that autoimmune conditions can dramatically impact on the course of disease with immediate need for treatment. The diagnosis of autoimmune anemia is not always easy to make, in this particular case the diagnosis of AIHA could never be clearly established due to the absence of a positive DAT while the patient had a low haptoglobin, elevated LDH and bilirubin. A DAT-negativity may be a consequence of low-affinity auto-antibodies, warm IgM, or IgA antibodies. The key finding in this case was the suppressed erythropoiesis in the bone marrow together with the almost absent reticulocyte count, However, pure red cell aplasia is a finding encountered in lymphoid neoplasms and should be differentiated from e.g. parvovirus infections. In this case, we had no information about parvovirus or T cell receptor rearrangement. The latter also indicates that PRCA lymphoma is at least in part caused by suppression of erythropoiesis by T cells. PRCA in lymphomas may occur alone or in conjunction with AIHA (Figure 1B).
As discussed above, ibrutinib is effective against CLL-associated AIHA in most cases. However, in this particular case the autoimmune condition did not respond to the BTK inhibitor, possibly due to a T-cell mediated mechanism. It only responded to adequate doses of steroids (and rituximab) given over a considerable period of time as also recommended for AIHA. It is important to use a dose of 1 mg/kg and not to taper the treatment too early. Subsequent treatment with ibrutinib in our patient was administered without problems and led to a CR of CLL. It is important to note that combined treatment with ibrutinib and steroids can lead to serious complications, in particular opportunistic infections (e.g. invasive fungal infections). This was the major reason why ibrutinib and prednisone were given sequentially.

Of note, steroid refractory PRCA responds to alemtuzumab, an anti-CD52 antibody previously used for CLL, but this should be reserved for salvage purposes. Anti-thymocyte globulin (ATG) has also been reported as an acceptable salvage therapy option.

**Cold agglutinin disease.** The pathophysiology of CAD is based on monoclonal IgM antibodies which trigger complement-mediated red cell lysis. This causes predominantly extravascular hemolysis in the liver. Effective removal of the B-cell clone and complement inhibition are therefore the therapeutic goals. For the reasons mentioned above, CAD does usually not respond to steroids or splenectomy. Rituximab or rituximab-containing regimens are very effective as first-line treatment (Table 1; Figure 1C). Rituximab monotherapy 375 mg/m2 for 4 weeks at 7-day intervals produces response rates of about 50%, although with few complete responses (CR). The median duration of response is less than one year, but repeat courses of rituximab are often effective in relapsed disease. A good option for primary CAD, particularly in the case of accompanying indolent lymphomas, are combinations of rituximab with fludarabine or bendamustine. We prefer R-bendamustine for its higher efficacy and rare induction of hemolytic events through the drug. Bortezomib is another effective drug in the setting of lymphomas. Ibrutinib has activity in Waldenström’s disease and can be tried as monotherapy. In case of AICs a CD20 monoclonal antibody may increase efficacy.

The other option for CAD is complement inhibition. The anti-C1s antibody sutimlimab effectively increased hemoglobin levels rapidly by more than 2 g/dL in 7 of 10 patients with a median best response of 3.9 g/dL. Inhibition of the complement cascade offers short-term relieve, but does not target the underlying clonal B-cell disease. However, it will be a good option in patients not
responding to rituximab or as bridging therapy. Sutimlimab can also be used in sequence with ibrutinib in patients with lymphoplasmacytic lymphoma with a \textit{MYD88} mutation.\textsuperscript{65,67} Clinical studies with other B-cell targeting agents such as \textit{PI3-Kinase-} or \textit{SYK-inhibitors} are ongoing.

\textbf{Patient 3}

A 63-year-old man presented with severe autoimmune hemolytic anemia after hip replacement. was prepared for hip replacement in January 2014. Postoperative hemoglobin was 7.8 g/dL with elevated reticulocyte $183 \times 10^9/L$, haptoglobin below detection limit and bilirubin of 2.8 mg/dL. LDH was elevated and a direct antiglobulin test (DAT) was positive for complement anti-C3d antibodies. The cold agglutinin titer was 64. The patient had an IgM kappa monoclonal protein, however with normal absolute IgM serum levels (209 mg/dL). The diagnosis of cold AIHA was made and on further hematologic workup, a slightly enlarged spleen was observed as well as an Ig kappa and IgHV rearrangement in the peripheral blood by PCR. The bone marrow examination revealed infiltration with a CD19, CD20 and CD5 positive but CD23 weak B-cell clone, classified as lymphoplasmacytic lymphoma with typical histology. Further investigation revealed that the B-cell clone carried a \textit{MYD88-L265P} mutation. The final diagnosis was lymphoplasmocytic lymphoma with cold agglutinins.\textsuperscript{48}

According to recommendations, the patient received 4 doses of 375 mg/m$^2$ rituximab in 4 consecutive weeks and the hemoglobin returned to 13.5 g/dL 6 weeks after start of infusion. Reticulocyte counts and haptoglobin normalized and the patient has now remained in complete hematologic remission for 5 years. The DAT is still positive for anti-C3d, which is often seen and in most definitions not part of the response criteria for AIHA.\textsuperscript{21}

\textbf{Immune thrombocytopenia}

ITP is a frequent autoimmune complication of CLL as well as other non-Hodgkin lymphomas.\textsuperscript{8,16,19,20,68} The diagnosis should be confirmed by a bone marrow biopsy according to diagnostic criteria for ITP.\textsuperscript{6,19,69} This is particularly important in CLL since the ITP may mimic bone marrow insufficiency. A discordance between hemoglobin and platelet counts should trigger the biopsy even if not required by CLL guidelines as well as further investigations including serum autoantibody assessment (which is not generally recommended).\textsuperscript{70} Treatment consists in immunosuppression with steroids according to ITP guidelines (Figure 1D).\textsuperscript{69} However, in the case of indolent B-cell lymphomas, the addition of rituximab or combinations thereof maybe beneficial due to the expected combined effect on AIC and
underlying disease. Given the fact that many patients with lymphoma have immunodeficiencies, intravenous immunoglobulin (IVIG) may also be beneficial. However, IVIG should be reserved for patients refractory to steroids and/or bleeding in whom a rapid increase in platelets is required. In addition, patients with recurrent infections are good candidates for IVIG. Response rates in CLL are around 50%. In non-responders, treatment with a thrombopoietin agonist should be considered. Response rates with eltrombopag in secondary ITP are as high as 81%. Rituximab with cyclophosphamide and dexamethasone is a good option to target both, the AIC as well as the lymphoma.

**Patient 4**

A 78-year old male patient with diagnosed with CLL in September 2012. At this time, he had a WBC of 41 x10^9/L. The patient was in good condition with a hemoglobin of 12.3 g/dL. However, thrombocytopenia of 38 x10^9/L was noted without symptoms of bleeding. The discrepancy between the almost normal hemoglobin and the low platelet counts triggered ITP diagnostics. No platelet-specific antibodies were found, but reticulated thrombocytes were clearly elevated (30.24%; normal values 2-9%). Thrombopoietin levels were within normal range (285 pg/mL, normal >150 pg/mL). These results, however not diagnostic, were compatible with increased platelet destruction. No anti-platelet antibodies were detected in peripheral blood. A bone marrow biopsy indicated a nodular infiltration with CLL cells (20%), but normal to elevated thrombopoiesis compatible with CLL and ITP. According to IWCLL Guidelines the patient was not treated against CLL in the absence of symptoms. The patient received 1 mg/kg of prednisolone for 3 days in preparation of surgery and the platelet count increased to 101 x10^9/L. Two years later the patient had an episode of severe gastrointestinal bleeding. The platelet count at this time was 20 x10^9/L with a WBC of 66 x10^9/L. Bone marrow biopsy was not performed at this time due to patients preference. Therefore, treatment with 6 cycles of rituximab + cyclophosphamide and dexamethasone (R 375 mg/m², C 750 mg/m², dexamethasone 12 mg absolute 5 days; R-CD) was chosen as first line therapy with the rationale to have a substantial effect on both conditions. As a result, his blood count returned to near normal values with WBC 7 x10^9/L, hemoglobin 12.4 g/dL and platelets 107 x10^9/L.

This case shows the efficacy of both, steroid monotherapy as well as Rituximab combination therapy (against both CLL and ITP). While not all ITP guidelines recommend a bone marrow biopsy for
diagnosis, this seem important in patients with an underlying lymphoma condition to determine the predominant reason of thrombocytopenia

**Evans Syndrome**

Evans syndrome is typically diagnosed in the 5th–6th decades and is secondary to underlying disorders, including lymphoproliferative diseases in 27 to 50%. It has been reported in up to 2.9% of a cohort of CLL patients.

Treatment is similar to that of secondary AIHA or ITP including the whole spectrum of immunosuppression and anti-lymphoma therapy.

**Autoimmune granulocytopenia**

Secondary autoimmune granulocytopenia or neutropenia (AIG) in lymphoma is a rare. AIG should be suspected in patients with declining neutrophil count not caused by other reasons (e.g., myelodysplastic syndromes, drugs, accompanying rheumatic diseases or infections). Typical examples include neutropenia in CLL, T-large granulocytic leukemia (T-LGL) or after CAR-T cell therapy. In particular, persistence of isolated neutropenia after chemotherapy or immunotherapy for longer than expected should trigger diagnostic work-up. AIG is sometimes hard to differentiate from long-term toxicities such as in CLL treated with fludarabine, cyclophosphamide and rituximab. Particularly, late onset neutropenia after anti-CD20 antibody therapy should be considered. In this case, bone marrow investigation and flow cytometry show reduced numbers of B-cells, T-lymphocyte imbalances as well as lower portions of myeloid progenitor cells. Diagnosis is clinical by exclusion and testing for anti-neutrophil antibodies is usually negative. Neutropenia may persist without symptoms for long, but infections are imminent. Four percent of patients with CLL-associated AIG presented with infections. Treatment options include G-CSF as well as immunosuppressive therapy (steroids). In T-LGL, the neutropenia frequently responds to low-dose methotrexate, cyclophosphamide or cyclosporin A. Rituximab used in the setting of rheumatic diseases is also effective.

**Autoimmune complications of antilymphoma treatment**

AIC may occur after treatment with agents other than chemoimmunotherapy, BTK or BCL2 inhibitors as described above. Stimulation of the immune system may have detrimental effects on a preexisting autoimmune condition. In most studies with immunomodulators or immune-checkpoint inhibitors, patients with
autoimmune diseases were excluded. We therefore have little knowledge about their actual effect. Nevertheless, we are very cautious with immunomodulators such as lenalidomide or PI3-Kinase inhibitors in patients with preexisting AIC and in most cases checkpoint inhibitors are avoided if possible. At least, close monitoring is advised. Immune-checkpoint inhibitors have hematologic as well as non-hematologic autoimmune side effects.\textsuperscript{62-84}

Finally, novel cellular therapies like CAR-T cell treatment against CD19 can cause prolonged cytopenias not attributable to late effects of chemotherapy or lymphodepletion. This should be differentiated from late myelodysplastic syndrome.\textsuperscript{85,86}

Other autoimmune complications

Hematologic AICs sometimes manifest themselves as coagulopathies. This may present with bleeding tendency as is the case in factor X deficiency, von Willebrand’s disease in lymphoplasmocytic lymphoma, or acquired hemophilia.\textsuperscript{87,88} We have also noted a close association of lupus anticoagulants with splenic marginal zone lymphomas which lead to frequent thrombotic events requiring prophylaxis or treatment.\textsuperscript{5}

Non-hematologic autoimmune conditions may precede the diagnosis of lymphoma for many years. These include Hashimoto’s thyreoiditis, rheumatologic diseases like systemic lupus erythematosus or rheumatoid arthritis, neurologic diseases such as polyneuropathy or gastrointestinal problems (celiac disease).\textsuperscript{5} C1-esterase deficiency is sometimes associated with lymphoma.\textsuperscript{89} Most of these diseases are B-cell driven and may also be asymptomatic. In many cases, workup of the autoimmune disease will include the search for malignancies, in particularly lymphomas.

Recently, the SARS-CoV2 pandemic and the development of efficient vaccines has posed new questions regarding the induction or exacerbation of AICs. Currently, it is recommended to vaccinate patients with AICs, but with special attention to these patients. We ask our patients to have their blood counts checked within one week after the vaccination whenever possible.\textsuperscript{90}

Course of autoimmune condition during and after antilymphoma treatment

The response of the autoimmune condition to anti-lymphoma treatment is dependent on the underlying AIC as well as on the type of treatment. In many instances, the autoantibodies and/or the clinical symptoms respond to anti-lymphoma treatment. Steroids as well as CD20 antibodies like rituximab or obinutuzumab are effective against many autoimmune diseases.
In a series of patients with lymphoma who received R-CHOP we documented the disappearance of rheumatic symptoms and RA antibodies. Similar results were obtained for acquired C1-esterase inhibitor deficiency. As discussed, ibrutinib and venetoclax seem to be beneficial in part by targeting both, the lymphoma as well as the AIC.

Conclusions and future developments

Autoimmune conditions can occur at any time before, during or after lymphoma diagnosis and treatment. AICs may be the indication for treatment either by immunosuppression or antineoplastic agents. Treatment is tailored towards the predominant disease (autoimmune or neoplastic) or both usually according to their respective guidelines or recommendations. Anti-CD20 antibodies have beneficial effects, particularly in B-cell lymphomas. Novel agents such as B-cell receptor inhibitors offer new possibilities for treatment. Some of these agents are even tested in specific trials against AICs. However, autoimmune conditions may also be triggered by some new treatment approaches against lymphoma, and will require adaptive clinical management.

AUTHOR RESPONSIBILITES

UJ and EP designed the manuscript, provided cases and wrote the manuscript.

CONFLICT OF INTEREST

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FIGURE LEGENDS:

Figure 1. Treatment algorithms for autoimmune cytopenias in lymphoma) Detailed regimens are given in Table 1.

(A) Warm autoimmune hemolytic anemia; (B) Pure red cell aplasia; (C) Cold agglutinine disease; (D) Immune thrombocytopenia; (E) Autoimmune granulocytopenia.
Table 1. Regimens used in the treatment of autoimmune cytopenias in lymphoma.

| Abbreviation | Therapy                                      | Dose                                                                 | References |
|--------------|----------------------------------------------|----------------------------------------------------------------------|------------|
| A            | Alemtuzumab                                  | 3 mg test dose then 10-30 mg/week for 4-6 weeks                      | 43         |
| ATG          | Anti-thymocyte globulin                      | 10-20 mg/kg for 10 days                                             | 45         |
| Az           | Azathioprine                                 | 0.5 mg/kg initial up to 2-2.5 mg/kg/day (max. 150 mg/day)            | 21         |
| B            | Bendamustine                                 | 70 or 90 or 100 mg/qm on the days 1-2 every 4 weeks                 | 28, 55, 59 |
| Bo           | Bortezomib                                   | 1.3 mg/qm weekly for 1-4 weeks                                       | 21, 55, 61 |
| C            | Cyclophosphamide                             | 1-2 mg/kg/day or 50-150 mg/day orally OR 300-1000 mg i.v. on day 1 every 4 weeks (e.g. 750 mg/day) | 13, 22, 26, 30-31 |
| CsA          | Cyclosporine A                               | 3-5 mg/kg/day                                                       | 19, 21     |
| ct/et        | Clinical trials / experimental therapies     | e.g. ibritinib 420 mg/day or venetoclax 400 mg/day after ramp-up weeks | 8, 20-21, 34-35, 41, 49, 55, 65 |
| D            | Dexamethason                                 | 40 mg for 4 days (monotherapy) OR 12 mg i.v. on days 1-2 and orally on days 3-7 (e.g. combined with rituximab and cyclophosphamide) | 11-13, 21-22, 30-31, 69 |
| Da           | Danazol                                      | 200 mg 3-4x/day                                                     | 21-22      |
| EPO          | Epoetin alpha                                | 5000-40000 units/week                                               | 44-45      |
| F            | Fludarabine                                   | 40 mg/qm days 1-5 or 25 mg/qm on days (1)-3                         | 22, 26, 55, 58 |
| GCSF         | Granulocyte colony stimulating factor        | 1-3 mcg/kg/day                                                      | 93         |
| HSCT         | hematopoietic stem cell transplantation       |                                                                      |            |
| IVIG         | intravenous immune globulin                  | 1-2 g/kg/day over 1-2 days (PRCA: 5 days)                            | 12-13, 19-20, |
| MMF          | Mycophenolat mofetil                         | 600 mg/qm 2x/day                                                    | 19, 21     |
| MTX          | Methotrexate                                  | 10 mg/qm weekly                                                     | 79         |
| P            | Prednisone                                   | 0.5-2 mg/kg/d for 4 weeks, taper over 1-2 months or                 | 11-13, 21-22, 69 |
| R            | Rituximab                                    | 375 mg/qm weekly for 4 weeks (or 100 mg weekly or 1000 mg on the days 1 and 15) | 12-13, 19, 21-22, 28, 30-31, 55-56, 58-59, 69 |
| Su           | Sutimlimab                                   | 10 mg/kg test dose, 60 mg/kg 4x/week starting 1-4 days after test dose | 55, 65     |
| TPO-RAs      | Thrombopoietin receptor agonists             | Eltrombopag 50-150 mg/day, Romiplostim 1-10 mcg/kg/week             | 69-70, 72  |
| V            | Vincristine                                  | 1 mg/week for 4-6 weeks                                             | 19, 32     |
Supportive care: red blood cell transfusions, if hemoglobin level < 8 mg/dL and/or symptomatic anemia.
Lower hemoglobin level might be tolerated in well adapted and/or young adults; higher hemoglobin levels needed in cases of additional heart diseases or symptomatic anemia in elderly.
Observe serum ferritin levels to avoid iron overload. Start iron chelation therapy if required.
Folic acid, osteoporosis treatment, thrombosis prophylaxis.