review

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Toxicities in B-cell non-Hodgkin lymphoma—new agents, new pitfalls

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Summary Immunochemotherapy has long been the backbone of all treatment for B-cell non-Hodgkin lymphoma. These therapies led to long-term disease control or even cure for some patients. However, these treatments also caused—sometimes severe—toxicities and deterioration of the quality of life. Novel agents targeting the B-cell-receptor pathway and bcl2 have made great inroads in the treatment of mature lymphoid neoplasms. These new agents present themselves with a wide variety of new toxicities, which have to be taken into account when being administered to our patients. Hematological toxicities are very common. All new agents lead to various levels of immune suppression or immune modulation, which is often not easily quantifiable. Opportunistic infections such as progressive multifocal leukoencephalopathy, pneumocystis pneumonia, other mycotic infections, cytomegalovirus infections and pneumocystis pneumonia have been described, sometimes with fatal outcome. Ibrutinib shows increased risk of atrial fibrillation. It also increases the risk of bleeding, making the proper anticoagulatory management of patients developing atrial fibrillation under treatment a challenge. Idelalisib causes severe, sometimes fatal immune-mediated end-organ toxicities, especially colitis, pneumonitis, and transaminitis. Copanlisib leads to metabolic changes, namely episodes of hyperglycemia and arterial hypertension. Venetoclax has caused clinically significant tumor lysis syndrome. The introduction of a prolonged ramp-up phase of step wise dose escalation has decreased the rate of clinically significant tumor lysis syndrome. The drug also causes high rates of hematological toxicities, especially neutropenia.

Keywords Ibrutinib · Idelalisib · Venetoclax · Tumor lysis syndrome · BTK inhibitor

Introduction

Non-Hodgkin lymphoma comprise a variety of malignant neoplasms derived from B-cells, T-cells, or NK-cells. They comprise 4.3% of all new cancer diagnoses and are the cause of 3.3% of all cancer deaths [1].

Immunochemotherapy has been the backbone of treatment of non-Hodgkin lymphoma for 20 years, leading to long-term disease control or even cure for some patients [2, 3]. However, this efficacy came at the price of sometimes severe toxicities.

In recent years, new targeted agents have increased their role in the treatment of non-Hodgkin lymphoma.

This review will focus on non-chemotherapeutic agents used in the treatment of non-Hodgkin lymphoma, including the Bruton's tyrosine kinase(BTK)-inhibitor ibrutinib, the phosphatidylinositol 3-kinase inhibitors idelalisib and copanlisib, and the BCL2-inhibitor venetoclax.

Ibrutinib

Ibrutinib is a Bruton tyrosine kinase inhibitor. It is indicated for the treatment of CLL in the first line in cases with a del17p or tP53 mutation. In all other CLL patients it is indicated when the patient has failed, or is deemed an unsuitable candidate for immunochemotherapy. It is also used in recurrent or refractory mantle cell lymphoma and Waldenstrom macroglobulinemia.

In single-agent ibrutinib therapies, grade 3–4 neutropenia occurred in approximately 15% of patients.

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Grade 3–4 thrombocytopenia occurred in approximately 10% of patients [4].

In a recently published retrospective analysis of 378 patients treated for various hematological disorders, serious (grade ≥3) infections occurred in 11% (43) of patients, including a surprisingly high portion of invasive fungal infections (27.2% of all serious infections) [5], among them PCP, cryptococcal infection and invasive aspergillosis. There have been case reports of PML [6]. Generally, ibrutinib moderately increases the risk of infection, and, if no other risk factors are present, anti-infectious prophylaxis is not indicated [7].

The most common non-hematological, non-infection adverse events include diarrhea, atrial fibrillation, hypertension, and bleeding/bruising [8].

Diarrhea, the most commonly observed AE, is mostly mild, and generally self-limited without additional therapy. Dose reduction or treatment discontinuation is only needed in a small minority of patients [8].

The risk of atrial fibrillation increases significantly under treatment with ibrutinib, with incidence rates of 5–8%. The risk to develop AF under ibrutinib treatment increases with the same risk factors as in the general population (hypertension, structural heart disease, male sex, age) [7].

The management of atrial fibrillation in patients with ibrutinib is challenging. If the severity according to CTCAE is ≥3, ibrutinib should be discontinued until control of AF, after which ibrutinib re-exposure is feasible. Even after a second relapse, a re-challenge at a lower dose can be considered [9]. Verapamil, diltiazem and amiodarone should be avoided due to drug–drug interactions with ibrutinib. The need for anti-coagulation due to atrial fibrillation needs to be balanced against the risk of bleeding, which is increased by ibrutinib. The CHA2DS2-VASC-Score and the HAS-BLED score may be valuable in determining the most beneficial course of action in these patients [10].

In early studies, both an increased overall bleeding risk and an increased risk of major bleeding was reported [11, 12].A recent meta-analysis found significantly increased risk of bleeding of any severity, but rates of major bleeding were not increased [13]. While vitamin-K antagonists were allowed initially in the first clinical studies, they were excluded from further trials after several intracerebral bleeding events [14].A portion of patients in subsequent trials used other anticoagulants and/or anti-platelet agents, and the rate of major bleeding events in these patients was low. However, there is no definitive study on the safety of the combination of anticoagulants and ibrutinib, and the individual risk has to be taken into account before starting such a patient with ibrutinib [14]. Therefore, patients already on non-optimally adjusted OAC for treatment of pre-existing AF should not be treated with ibrutinib, and, even in patients with a well-controlled anti-coagulation therapy, treatment alternatives, e. g. rituximab/idelalisib or venetoclax should be considered. Also, in patients with a history of major bleeding due to a cause which can not be adequately treated or modified, ibrutinib should be avoided.

Idelalisib

Idelalisib is a phosphatidylinositol-3-kinase inhibitor used in the treatment of CLL and refractory follicular lymphoma.

It has shown strong efficacy in these indications, but severe toxicities have hampered its use.

Rates of severe neutropenia in clinical trials were approximately 30%. However, the rates of febrile neutropenia were low (3%) [15, 16].

In a retrospective analysis, 2.5% of patients under idelalisib treatment developed PCP [17], leading to the recommendation of PCP prophylaxis for all patients from start of idelalisib therapy up to 2–6 months after discontinuation [7] Similarly, an increased rate of CMV infections has been noted, and regular CMV monitoring should be performed [7].

Immune-mediated colitis usually appears as watery diarrhea [18]. In all, 14–19% of all patients receiving idelalisib develop grade 3–5 diarrhea [9]. Idelalisib-caused diarrhea can be separated into two groups: an early (usually within the first 2 months of treatment), self-limiting form which responds well to anti-motility drugs, and a late, more severe form which does not respond to anti-motility drugs [9].

In grade 1 and 2 diarrhea, idelalisib may be continued, and symptomatic treatment is advised. However, grade 2 diarrhea occurring late or not responding to anti-motility drugs should be treated similar to more severe forms. In patients with grade 3 or 4 diarrhea, or those with grade 2 diarrhea not responding to treatment, idelalisib should be immediately discontinued, and workup to exclude infectious causes should be performed. Once infectious causes are excluded, treatment with topical and/or oral and/or intravenous steroids should be started. After diarrhea resolves, in grade 2–3 diarrhea, idelalisib may be reinstated at a lower dose per clinical judgment in individual cases. Prophylactic concomitant use of budesonide may be warranted [19].

Pneumonitis has been seen at rate of approximately 4% in patients receiving idelalisib, and several fatal cases have been reported [9]. Therefore, extreme caution has to be taken in patients under treatment reporting respiratory symptoms. If a mild persistent cough, a 5% drop in oxygen saturation, increased dyspnea under exertion, or pulmonary infiltrates in imaging occur, idelalisib should be discontinued immediately, and patients should undergo a comprehensive workup including a high-resolution chest CT. Bronchoscopy and BAL needs to be evaluated individually. Systemic prednisolone should be started at a dose of

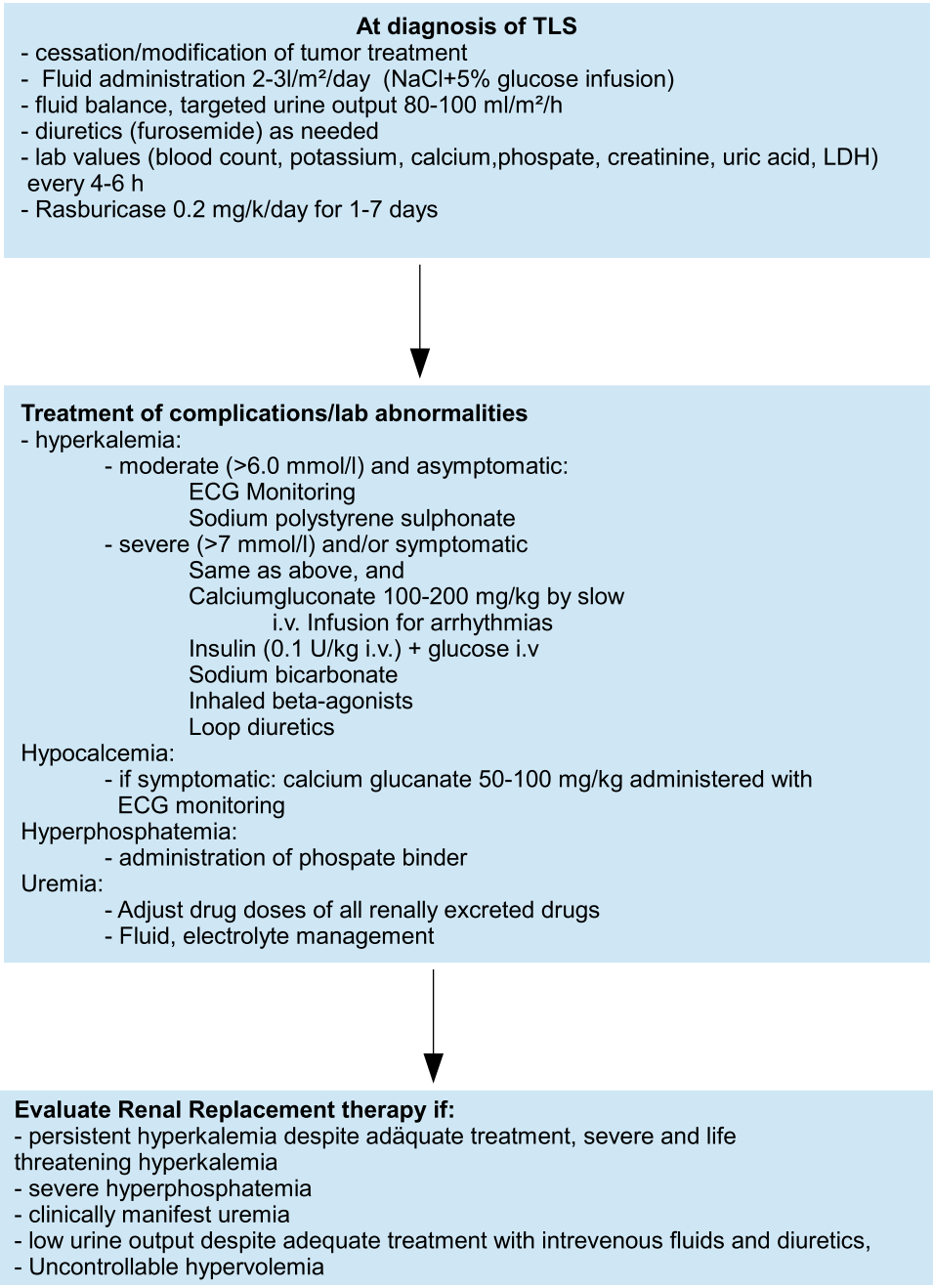

Fig. 1 Treatment algorithm for tumor lysis syndrome. *TLS* tumor lysis syndrome, *LDH* lactate dehydrogenase, *ECG* electrocardiography

1 mg/kg immediately, while the patient undergoes an infection workup. Idelalisib should not be restarted in patients with possible autoimmune pneumonitis [18].

Serious hepatotoxicity has occurred in 14% of patients, and fatal cases of liver failure have happened [18]. Liver function tests should be performed every 2 weeks in the first 3 months of therapy, followed by monthly monitoring. In patients with AST/ALT elevation 3–5 times the upper limit of normal (ULN), patients can continue receiving idelalisib under weekly monitoring, while patients with transaminases at levels 5–20 times ULN should discontinue idelalisib until normalization of transaminases, after which treatment can be commenced at a lower dose. Patients with transaminases >20 times ULN should permanently stop treatment with idelalisib [9].

Copanlisib

Copanlisib is a phosphatidylinositol-3-kinase inhibitor used in the treatment of follicular lymphoma.

The toxicity profile of copanlisib is different from idelalisib [20]. While grade 3–4 neutropenia occurred at a similar rate (24%) to idelalisib, the rate of autoimmune complications were substantially lower. Only 8% of patients developed non-infectious respiratory symptoms, with only 1% developing grade 3 pneumonitis, while 1% developed non-infectious colitis.

While elevated transaminases were frequent (28%), grade 3 and grade 4 liver toxicity was seen in 1% of patients each.

Transient hyperglycemia occurred in 50% of all patients. In cases of fasting serum glucose levels <200 mg/dl, copanlisib should be held. If pre- or posttreatment serum glucose is >500, dose reduction in 15 mg steps is indicated [18].

Arterial hypertension manifested itself in 30%. In grade 2 and grade 3 hypertension, anti-hypertensive therapy should be initiated or increased. Severe hypertension (>200/110 mm Hg) and signs of end organ damage should lead to immediate discontinuation of treatment.

Venetoclax

Venetoclax is used in the treatment of CLL with 17p deletion or tp53 mutation in patients relapsing after, or not suitable for, B-cell-receptor-targeted therapy, and in patients without this high risk mutation after treatment failure following both immunochemotherapy and BCR-targeted therapy. Its use in a wide variety of hematological malignancies, including multiple myeloma, diffuse large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, and acute myeloid leukemia, is studied.

Venetoclax shows substantial hematological toxicity, with grade 3–4 neutropenia in 40% when used as a single agent [21, 22], and 58% in combination with rituximab [23]. However, rates of febrile neutropenia were low (4–5%). The rates of opportunistic infections under venetoclax therapy were low, and no prophylaxis is recommended [9].

The clinically most important non-hematological non-infection toxicity is tumor lysis syndrome.

In a phase 1 study of venetoclax in CLL, several cases of severe tumor lysis syndrome (TLS) occurred, including a fatal case [24]. This led to a modification of drug administration with an increase in length of the ramp-up schedule at initiation of treatment. Using this schedule in the following treatment, the TLS that occurred in 3–5% of patients was easily controlled and resolved without sequelae [21–23].

Before any patient is started on venetoclax, risk of TLS should be assessed. Important risk factors for tumor lysis syndrome include high tumor burden (lymph nodes >5 cm, absolute lymphocyte count $>25 \times 10^9$), renal dysfunction, and high uric acid levels pretreatment. While in patients with low risk of tumor lysis syndrome, oral hydration ± allopurinol may be sufficient, in patients with increased risk of TLS, intravenous prehydration should be performed. Additionally, patients with high risk of tumor lysis syndrome should receive either allopurinol/febuxostad or rasburicase, depending on risk.

The ramp-up schedule has to be followed meticulously. The patient has to be started at a dose of 20 mg/day for one week, followed by a week of 50 mg, 100 mg, and 200 mg each, before arriving at a dose of 400 mg, which then is given for the duration of the treatment. At least the first dose of venetoclax and the first administration of the 50 mg dose should be given in an in-patient setting. Every patient who is considered to be at increased risk of TLS should also be treated in an in-patient setting for subsequent dosage increases.

Lab values (blood count, potassium, calcium, phosphate, creatinine, uric acid, LDH) should be closely monitored, at least both 6 h before and 12–24 h after administration of the first dose, and in daily intervals going forward. In patients with increased risk of tumor lysis syndrome, lab values should be checked 6–8 h after first administration of venetoclax. Fluid balance has to be monitored meticulously. In patients developing laboratory or clinical evidence of tumor lysis syndrome, venetoclax should be paused immediately, and treatment should be performed according to published guidelines ([25]; Fig. 1). If laboratory and clinical evidence of TLS resolves within 24–48 h, therapy can be restarted at the same dose. If signs persist for longer than 48 h, therapy has to be restarted at a lower dose, and only after complete resolution of the TLS. Patients having experienced TLS should be closely monitored, and treated in an in-patient setting in subsequent dosage increases.

Conclusion

The new agents used in the treatment of mature B-cell neoplasms show remarkable efficacy. For these agents, long-term safety data are still very limited. They, in combination with CD20 antibodies, offer the possibility of chemotherapy-free treatment for our patients. However, while generally well tolerated, the new agents cause a widely different spectrum of complications.

In patients with ibrutinib, monitoring of bleeding risk is essential, as is proper management of atrial fibrillation once it occurs.

Idelalisib, while highly effective, causes both severe infectious complications as well as possibly life-threatening autoimmune-mediated organ toxicities, leading to a limitation of its use, and the need of very strict monitoring to prevent life-threatening complications.

Patients receiving venetoclax have to be closely monitored for signs of tumor lysis syndrome, especially at the beginning of treatment. Regular blood counts are mandatory to recognize neutropenia in time.

Taking these proper precautions allows the safe and effective administration of these exciting new drugs.

Conflict of interest T. Spanberger declares that he has no competing interests.

References

1. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER cancer statistics review, 1975-2015. Bethesda: National Cancer Institute; 2018. based on November 2017 SEER data submission, posted to the SEER web site. https://seer.cancer.gov/csr/1975_2015.
2. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116–v25.
3. Schulz H, Bohlius J, Skoetz N, et al. Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Cochrane Database Syst Rev. 2007; https://doi.org/10.1002/14651858.cd003805.pub2.
4. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507–16.
5. Varughese T, Taur Y, Cohen N, et al. Serious infections in patients receiving Ibrutinib for treatment of lymphoid cancer. Clin Infect Dis. 2018; https://doi.org/10.1093/cid/ciy175.
6. Raisch DW, Rafi JA, Chen C, Bennett CL. Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA's adverse event reporting system. Expert Opin Drug Saf. 2016;15(8):1003–11.
7. Reinwald M, Silva JT, Mueller NJ, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). Clin Microbiol Infect. 2018;24(Suppl 2):S53–S70.
8. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125(16):2497–506.
9. Rhodes J, Mato A, Sharman JP. Monitoring and management of toxicities of novel B cell signaling agents. Curr Oncol Rep. 2018;20(6):49.
10. Vrontikis A, Carey J, Gilreath JA, Halwani A, Stephens DM, Sweetenham JW. Proposed algorithm for managing Ibrutinib-related atrial fibrillation. Oncology (Williston Park, NY). 2016;30(11):970–4–980–1, C3.
11. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213–23.
12. Jaglowski SM, Jones JA, Nagar V, et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. Blood. 2015;126(7):842–50.
13. Caron F, Leong DP, Hillis C, Fraser G, Siegal D. Current understanding of bleeding with ibrutinib use: a systematic review and meta-analysis. Blood Adv. 2017;1(12):772–8.
14. Boriani G, Corradini P, Cuneo A, et al. Practical management of ibrutinib in the real life: focus on atrial fibrillation and bleeding. Hematol Oncol. 2018; https://doi.org/10.1002/hon.2503.
15. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370(11):1008–18.
16. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370(11):997–1007.
17. Sehn LH, Hallek M, Jurczak W, Brown JR, Barr PM, Catalano J, Coutre SE, Furman RR, Lamanna N, Loïc Y, Zelenetz AD, Sharman JP, DeVos S, Adewoye AH, Yeonhee K, Flinn IW, Salles GA. A retrospective analysis of pneumocystis Jirovecii pneumonia infection in patients receiving Idelalisib in clinical trials. Blood. 2018;128(22):3705. http://www.bloodjournal.org/content/128/22/3705.
18. Greenwell IB, Ip A, Cohen JB. PI3K inhibitors: understanding toxicity mechanisms and management. Oncology (Williston Park, NY). 2017;31(11):821–8.
19. Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma. 2015;56(10):2779–86.
20. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by Copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol. 2017;35(35):3898–905.
21. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17(6):768–78.
22. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of Venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. J Clin Oncol. 2017;35(8):826–33.
23. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378(12):1107–20.
24. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with Venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):311–22.
25. Coiffier B, Altman A, Pui C-H, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767–78.