Antithrombotic prophylaxis in patients treated with Bruton's tyrosine kinase inhibitors

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ABSTRACT

There is an increased risk of atrial fibrillation in patients treated with Bruton's tyrosine kinase inhibitors such as ibrutinib or acalabrutinib. The risk of this complication, as in the general population, increases with the age of patients and the coexistence of cardiovascular diseases. Due to the observed platelet dysfunction associated with the activity of ibrutinib, antithrombotic prophylaxis against stroke becomes an important clinical problem. The presence of potential interactions between ibrutinib and oral anticoagulant and additionally increased risk of bleeding determine specific therapeutic choices, which are described in the article.

Key words: ibrutinib, anticoagulants, bleeding, stroke, atrial fibrillation

INTRODUCTION

Ibrutinib is approved by the European Medicines Agency (EMA) for the following hematological indications: 1) as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL); 2) as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL); 3) as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy; 4) as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy, and 5) in combination with rituximab is indicated for the treatment of adult patients with WM.

Acalabrutinib is approved: 1) as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), and 2) as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Ibrutinib therapy is associated with the risk of bleeding diathesis, infection, as well as hypertension, atrial fibrillation, and heart failure [1–3]. The incidence of symptomatic atrial fibrillation is similar for ibrutinib and acalabrutinib, both drugs also trigger atrial fibrillation with similar frequency in the elderly (> 75 years) and those with a history of paroxysmal atrial fibrillation, and patients with comorbid cardiovascular diseases are particularly predisposed [4].

The latest European Society of Cardiology (ESC) recommendations, prepared in cooperation with the European Hematology Association (EHA), indicate that there is currently insufficient data to develop separate cardiac algorithms for ibrutinib and acalabrutinib because the profile and rate of cardiovascular complications, including the rate of atrial fibrillation, appear to be similar for both drugs [5].

IBRUTINIB AND ATRIAL FIBRILLATION

Bruton's tyrosine kinase (BTK) inhibitors are used in hematological diseases usually diagnosed in the elderly, and age itself is an important risk factor for atrial fibrillation

[6]. Concomitant diseases in the elderly additionally increase the risk of atrial fibrillation [7]. The presence of this arrhythmia is predicted by the presence of left atrial enlargement [8, 9].

Because atrial fibrillation is associated with the risk of developing heart failure and experiencing a stroke, diagnostic vigilance for this arrhythmia is recommended at every physician visit for patients treated with ibrutinib or acalabrutinib, at least by measuring the regularity of the heart rhythm during physical examination or electrocardiography (class of recommendation I, level of evidence C).

In cardio-oncology, the following factors increasing the risk of bleeding are mentioned: gastrointestinal (GI) cancers, cancers of the genitourinary system, thrombocytopenia, platelet dysfunction in the course of hematological diseases or bone marrow suppression, advanced age, renal or hepatic dysfunction, metastatic cancer, low body mass index (BMI), **therapy with ibrutinib**, and with vascular endothelial growth factor (VEGF) inhibitor (especially bevacizumab) or cetuximab [10, 11].

HOW TO PLAN ANTICOAGULATION IN HEMATOLOGY IN PATIENTS WITH ATRIAL FIBRILLATION?

Based on the available knowledge in planning anticoagulation in cancer patients, the authors of the ESC guidelines proposed the TBIP algorithm, labeling the steps as T (thrombotic risk), B (bleeding risk), I (drug interactions), P (patient preferences) [12].

The CHA_2DS_2-VASc score, which is widely known and used in cardiology, has not been adequately validated in cancer patients, especially in terms of the definition of a low-risk patient, i.e. not requiring thromboprophylaxis [13]. Some observations indicate that in the course of neoplastic diseases, the CHA_2DS_2-VASc score equal to 0 or 1 is associated with a higher risk of stroke than in the population without cancer [14]. It seems that the CHA_2DS_2-VASc score does not allow for the estimation of prothrombotic risk, because it does not take into account factors related to cancer and its treatment.

The ESC guidelines clearly indicate that long-term thromboprophylaxis in atrial fibrillation in a cancer patient:

- is recommended when the CHA_2DS_2-VASc score is at least 2 (male) or at least 3 (female);
- should be considered when the CHA_2DS_2-VASc score is 1 (male) or 2 (female);
- may be considered when the CHA_2DS_2-VASc score is 0 (male) or 1 (female).

When deciding on chronic anticoagulation in cancer, it should be borne in mind that, on the one hand, in the case of effective anti-cancer treatment, the prothrombotic risk may decrease, but, on the other hand, in the case of cancer progression or toxicity, especially hematological, the risk of bleeding may increase. Therefore, the thrombotic risk and bleeding risk should be reassessed periodically in relation to the type of histopathological diagnosis, clinical stage, and prognosis resulting from the response to the anticancer treatment [15]. According to the ESC guidelines, such a periodic assessment of the benefits of anticoagulation against the risk of bleeding in cancer patients with concomitant atrial fibrillation has the highest class I recommendation (level of evidence C).

New oral anticoagulants (NOACs) (in alphabetical order: apixaban, dabigatran, edoxaban, rivaroxaban) should be considered as the preferred option for thromboprophylaxis in atrial fibrillation coexisting with cancer (class of recommendations IIa, level of evidence B). In situations where oral anticoagulation cannot be used, low-molecular-weight heparin (LMWH) should be considered — according to the ESC guidelines, this is also a recommendation class IIa, but the level of evidence is C, i.e. expert opinion [5]. The efficacy of LMWHs in preventing stroke in atrial fibrillation has not been proven and their use is based on efficacy and safety observed in venous thromboembolism. It is assumed by default that LMWHs in this indication should be used in therapeutic doses (e.g. enoxaparin 1 mg/kg subcutaneously every 12 h or 1.5 mg/kg subcutaneously once a day). They should be used as an alternative option when patients cannot take oral anticoagulants [16]. This is understood as the inability of these patients to take drugs orally due to the cancer's advanced stage, i.e., for example, impaired absorption of drugs from the upper GI tract. So-called bridging therapy should not be used routinely when invasive diagnostics are performed. The ESC guidelines define several clinical situations in which LMWH should be preferred, i.e.: unoperated GI or genitourinary cancer, significant gastroenterological diseases, GI toxicity of cancer therapy, severe renal dysfunction (creatinine clearance [CrCl]) < 15 mL/min), interactions between NOACs and anticancer drugs, platelet count below 50 G/L.

The dosing of LMWH in the case of recent active bleeding or significant thrombocytopenia in medical history is a difficult and completely individual decision.

In June 2022, the EHA, in cooperation with the ESC, published recommendations on anticoagulant treatment in patients with cancer complicated by thrombocytopenia [17]. In the case of grade 4 thrombocytopenia (platelet count < 25 G/L), whether for prophylaxis in atrial fibrillation or chronic treatment of venous thromboembolism, it is recommended that anticoagulants be withheld (in acute conditions based on an individual assessment). However, in the case of grade 3 thrombocytopenia (platelet count 25–50 G/L):

- the use of oral anticoagulants is discouraged, both in the case of venous thromboembolism and atrial fibrillation;
- it is recommended to **withhold** ongoing anticoagulation in patients with atrial fibrillation in case of **expected short-term thrombocytopenia** unless the patient is at very high thrombotic risk or has additional cancer-related thrombotic risk factors;

- in patients with atrial fibrillation at a very high risk of thrombosis, reducing the therapeutic dose of LMWH by 50% (e.g. enoxaparin 0.5 mg/kg subcutaneously every 12 h) with close monitoring of the platelet count **may be considered** in the case of stable grade 3 thrombocytopenia that persists from weeks to months;
- for patients with atrial fibrillation and a mechanical heart valve with a stable platelet count of 40–50 G/L, treatment with a vitamin K antagonist (VKA) with a target international normalized ratio (INR) of 2 **should be considered**;
- in patients with atrial fibrillation and a mechanical heart valve with a platelet count of 25–40 G/L or observed non-therapeutic INR, LMWH at a therapeutic dose reduced by 50% **may be considered** (e.g. enoxaparin 0.5 mg/kg subcutaneously every 12 h).

THE BLEEDING RISK ASSOCIATED WITH IBRUTINIB

Bleeding observed in patients treated with ibrutinib is mainly related to the activity of this drug, and not only to the underlying hematological disease in the course of which thrombocytopenia coexists, as well as to comorbidities requiring antiplatelet or antithrombotic therapy [18–21]. Pharmacological inhibition of BTK by ibrutinib has been shown to affect the function of glycoprotein VI and platelet adhesion-dependent on collagen and von Willebrand factor [22]. Bleeding is most often observed during the first months of ibrutinib therapy, exactly during the first 6 months, then the risk decreases [23]. It should be remembered that the most common hematological complications of ibrutinib, at least grade 3, include neutropenia, anemia, and thrombocytopenia, which increases the risk of bleeding [24].

Based on the available meta-analysis, it can be concluded that the risk of bleeding of any degree is approximately 3-fold increased (relative risk [RR] 2.93; 95% confidence interval [CI]: 1.14–7, 52; p = 0.03) in patients receiving ibrutinib [25]. Data from the Surveillance, Epidemiology, and End Results (SEER) — Medicare Cancer Registry database show that up to 18% of patients with CLL experienced at least one major bleeding [26]. This indicates the need to make special caution in patients receiving additional anticoagulants or antiplatelet drugs.

One of the studies analyzed the risk of bleeding among patients taking ibrutinib and concomitant anticoagulant or antiplatelet drug [27]. Bleeding events were defined as major if they were at least grade 3 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 when intraocular bleeding resulted in a loss of vision, required transfusion of at least 2 units of packed red cells, resulted in hospitalization or when there was intracranial bleeding. Anticoagulants (11%) or antiplatelet agents (34%) or both (9%) were commonly used concomitantly during ibrutinib therapy. The most common anticoagulant was LMWH (15%), although it was often used for a limited time (< 3 months in 33 of 48 patients), often in a prophylactic dose. The most commonly used antiplatelet drugs were acetylsalicylic acid (ASA) (21%), and many patients received non-steroidal anti-inflammatory drugs (NSAIDs; 28%). The only predictor of mild bleeding in the multivariate analysis was **prior bleeding of any grade** (analyses included the use of anticoagulants/antiplatelet drugs, age, platelet count, bleeding history, risk of falls, use of cytochrome P inhibitors, baseline liver, and kidney function). Of the 175 patients who received anticoagulant or antiplatelet drugs, 5 (3%) experienced major bleeding: 1 patient received heparin, 1 patient received ASA, 1 patient received NSAID, 1 patient received warfarin + ASA, 1 patient received heparin + NSAID.

Although the risk of bleeding with ibrutinib is increased, post hoc analyzes of clinical trials did not reveal significant differences with or without additional anticoagulants or antiplatelet medications [28].

HOW TO PLAN ANTICOAGULATION IN PATIENTS TREATED WITH IBRUTINIB?

A panel of European hematology experts prepared the principles of management for various complications of ibrutinib, including cardiac problems [29].

Acetylsalicylic acid is the antiplatelet agent most commonly used in combination with ibrutinib, but patients should be closely monitored and ASA should be discontinued if bleeding occurs. Although ibrutinib has some antiplatelet activity, there is insufficient evidence to suggest that it can replace ASA in its classic cardiac indications (i.e., prevention of coronary events) [30].

The combination of ibrutinib with dual antiplatelet therapy, even if it is ASA and clopidogrel, may result in major bleeding due to different mechanisms of blocking platelet aggregation. Therefore, most experts believe that one of the antiplatelet drugs should be discontinued if treatment with ibrutinib is required. In case a patient is treated with ibrutinib and must undergo coronary intervention, ibrutinib therapy should be interrupted for the duration of dual antiplatelet therapy. The duration of dual antiplatelet therapy should be individually defined in this situation and possibly shortened if ibrutinib needs to be restarted.

In the early studies on ibrutinib, concomitant use of VKAs (warfarin, acenocoumarol) was excluded [31–33]. However, the use of NOACs was allowed. Therefore, the use of NOACs in this population is assumed to be preferred in patients with classic indications for anticoagulation — anticoagulation is recommended when the CHA_2DS_2-VASc score is at least 2 (it should be considered when the CHA_2DS_2-VASc score = 1). ASA should not be used in the prevention of strokes in atrial fibrillation [34].

Currently, there are no clear recommendations as to which oral anticoagulant should be preferred. Rivaroxaban, apixaban, and ibrutinib are metabolized by CYP3A4 and are also substrates or inhibitors of P-glycoprotein (P-gp).

Theoretically, if P-gp is inhibited and the CYP3A4 pathway is fully saturated, then ibrutinib when used with CYP3A4 substrates could lead to an increase in plasma concentrations of apixaban or rivaroxaban, but this is unlikely to be clinically relevant. It is hypothesized that P-gp inhibition by ibrutinib may affect dabigatran and edoxaban concentrations, but there are no clinical data to support this. Most authors indicated that apixaban would be the preferred option. The authors indicate the use of a classic dose of 5 mg orally twice a day; dose reduction to 2.5 mg orally twice daily is reserved for different subgroups of patients, for example, those with renal insufficiency, body weight less than 60 kg, or those over 80 years of age. An additional advantage of apixaban is its milder profile of side effects from the GI tract. Dabigatran would be the second suggested NOAC; the authors recommend administration in a standard dose of 150 mg orally twice a day, a reduced dose (110 mg orally twice a day) may be considered in patients at high risk of bleeding or with renal failure. Authors favoring dabigatran highlight the availability of an antidote and the reduced potential for CYP3A4 interaction as justification for the choice of treatment. None of the authors singled out rivaroxaban or edoxaban as the preferred NOAC in patients treated with ibrutinib. On-going anticoagulation should not be a reason to reduce the ibrutinib dose.

In another document prepared by Australian experts [35], it was emphasized that all currently available NOACs have the potential for pharmacological interactions with ibrutinib. However, the effect of ibrutinib on the metabolism of anticoagulants via P-gp inhibition is of greater concern than the effect of NOACs on ibrutinib concentrations. Greater potential concerns are associated with dabigatran. Dabigatran is not metabolized and does not inhibit or induce any CYP isoform. However, a prodrug of dabigatran (dabigatran etexilate) is a substrate for P-gp and an interaction based on the potential inhibition of P-gp by ibrutinib is possible. Concomitant administration of potent P-gp inhibitors or inducers has been shown to affect the conversion of the prodrug to the active dabigatran and may affect its plasma concentration. The problem is the effect of kidney function on metabolism and the potential additive effect on platelet function. Dabigatran, by inhibiting factor II, may have an inhibitory effect on platelet function as well as other intracellular signaling and cytokine pathways that are activated by factor II. The experts considered that dabigatran was therefore the least favored NOAC in this indication [35].

The use of apixaban or rivaroxaban seems more appropriate. Given the potential risk of increased plasma levels, it is recommended to use the lowest effective dose of the anticoagulant. Although ibrutinib, apixaban, and rivaroxaban are substrates of CYP3A4, the use of the two substrates poses only a conceptual risk that ibrutinib may increase plasma concentrations of apixaban or rivaroxaban due to its potential to inhibit CYP3A4 and P-gp, however, it is considered unlikely that to be clinically significant. In contrast, neither apixaban nor rivaroxaban affects the metabolism of ibrutinib.

The authors emphasized that opinions on the use of VKA are divided. Both ibrutinib and warfarin are primarily metabolized by cytochrome P450 enzymes with moderate

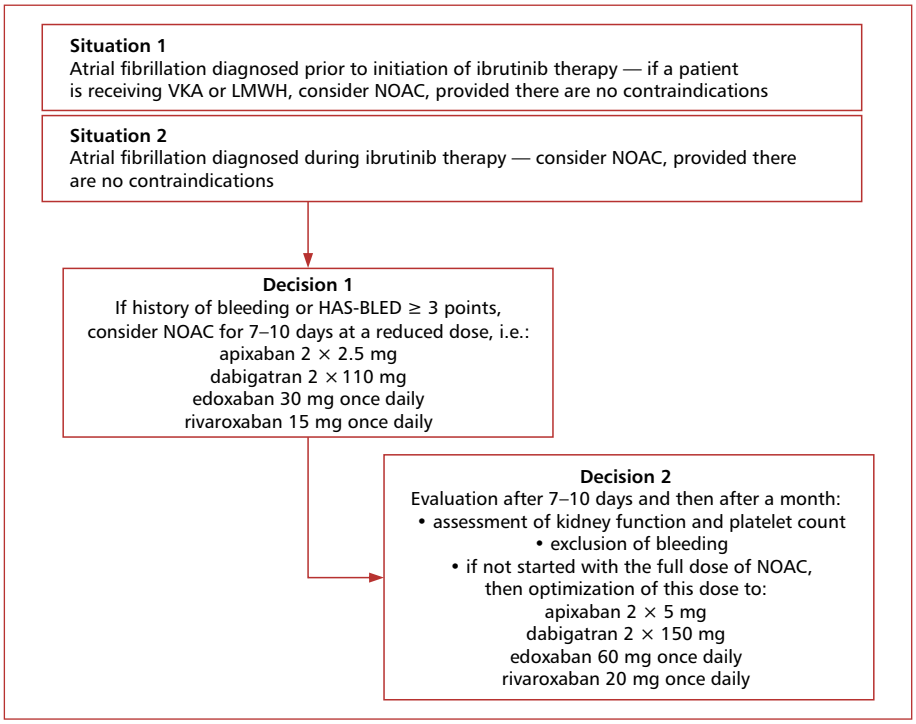

Figure 1. Suggested algorithm for initiating thromboprophylaxis with new oral anticoagulants (based on the opinion of Italian experts [36]); LMWH — low-molecular-weight heparin; NOAC — new oral anticoagulant; VKA — vitamin K antagonist

potential for interaction. Warfarin is mainly metabolized by CYP2C9 with minor contributions from other CYP enzymes including CYP3A4. While a pharmacological interaction is possible, it should be emphasized that warfarin can be used in justified cases (such as the presence of metal valves), provided that a therapeutic INR can be achieved.

A group of Italian experts composed of hematologists, cardiologists, and pharmacologists [36] emphasizes that there is a lack of good-quality data on the long-term use of LMWH in patients treated with ibrutinib. Therefore, oral anticoagulants should be considered in long-term thromboprophylaxis. In the countries of the European Union, the use of VKA is rather not recommended (except in exceptional situations). However, data on the use of NOACs in patients receiving ibrutinib are also limited [37, 38]. In this document, experts emphasize that anticoagulation should be started with the lowest effective dose in order to minimize the risk of bleeding. Patients with a HAS-BLED score greater than 3 in the first 7–10 days should be considered for apixaban 2.5 mg orally every 12 h, or dabigatran 110 mg orally every 12 h, or edoxaban 30 mg orally once daily, or rivaroxaban 15 mg orally once daily (Figure 1). The patient should be instructed to report all bleeding episodes. In case of major or clinically significant bleeding, NOACs should be withheld.

Heart rhythm-controlling medications such as beta-blockers or digoxin do not interact with ibrutinib, but verapamil and diltiazem are contraindicated. Amiodarone should be avoided, but if it is used, dabigatran or edoxaban may be preferred to apixaban or rivaroxaban for anticoagulation [36]. According to Italian experts, amiodarone as a CYP3A4 substrate may increase the concentration of ibrutinib, and thus increase the risk of cardiotoxicity and bleeding, while the anticoagulant effect of apixaban and rivaroxaban may also be increased.

SUMMARY

The decision to start thromboprophylaxis and the choice of oral anticoagulant in patients receiving BTK inhibitors should always be personalized. The basic selection criterion should be the estimated risk of bleeding resulting partly from the effect of ibrutinib on platelet function and from possible pharmacokinetic interactions with oral anticoagulant.

Additional information

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REFERENCES

1. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017; 102(10): 1796–1805, doi: 10.3324/haematol.2017.171041, indexed in Pubmed: 28751558.
2. Löpez-Fernández T, Canales M, Farmakis D, et al. Ibrutinib-associated atrial fibrillation: a practical approach. Ann Hematol Oncol. 2018; 5(4): 1203, doi: 10.26420/annhematoloncol.2018.1203.
3. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. J Am Coll Cardiol. 2019; 74(13): 1667–1678, doi: 10.1016/j.jacc.2019.07.056, indexed in Pubmed: 31558250.
4. Brown JR, Byrd JC, Ghia P, et al. Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients. Haematologica. 2022; 107(6): 1335–1346, doi: 10.3324/haematol.2021.278901, indexed in Pubmed: 34587719.
5. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022; 43(41): 4229–4361, doi: 10.1093/eurheartj/ehac244, indexed in Pubmed: 36017568.
6. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017; 58(7): 1630–1639, doi: 10.1080/10428194.2016.1257795, indexed in Pubmed: 27885886.
7. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
8. Lentz R, Feinglass J, Ma S, et al. Risk factors for the development of atrial fibrillation on ibrutinib treatment. Leuk Lymphoma. 2019; 60(6): 1447–1453, doi: 10.1080/10428194.2018.1533129, indexed in Pubmed: 30730240.
9. Mato AR, Clasen S, Pickens P, et al. Left atrial abnormality (LAA) as a predictor of ibrutinib-associated atrial fibrillation in patients with chronic lymphocytic leukemia. Cancer Biol Ther. 2018; 19(1): 1–2, doi: 10.1080/15384047.2017.1394554, indexed in Pubmed: 29281559.
10. Menapace LA, McCrae KR, Khorana AA. Predictors of recurrent venous thromboembolism and bleeding on anticoagulation. Thromb Res. 2016; 140 Suppl 1: S93–S98, doi: 10.1016/S0049-3848(16)30106-2, indexed in Pubmed: 27067987.
11. Angelini DE, Radivoyevitch T, McCrae KR, et al. Bleeding incidence and risk factors among cancer patients treated with anticoagulation. Am J Hematol. 2019; 94(7): 780–785, doi: 10.1002/ajh.25494, indexed in Pubmed: 31006890.
12. Pastori D, Marang A, Bisson A, et al. Thromboembolism, mortality, and bleeding in 2,435,541 atrial fibrillation patients with and without cancer: A nationwide cohort study. Cancer. 2021; 127(12): 2122–2129, doi: 10.1002/cncr.33470.
13. Boriani G, Lee G, Parrini I, et al. Council of Cardio-Oncology of the European Society of Cardiology. Anticoagulation in patients with atrial fibrillation and active cancer: an international survey on patient management. Eur J Prev Cardiol. 2021; 28(6): 611–621, doi: 10.1093/eurjpc/zwaa054, indexed in Pubmed: 33624005.
14. D'Souza M, Carlson N, Fosbøl E, et al. CHA_2DS_2-VASC score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. Eur J Prev Cardiol. 2018; 25(6): 651–658, doi: 10.1177/2047487318759858, indexed in Pubmed: 29482441.
15. López-Fernández T, Martín-García A, Roldán Rabadán I, et al. Expert reviewers. Atrial fibrillation in active cancer patients: expert position paper and recommendations. Rev Esp Cardiol (Engl Ed). 2019; 72(9): 749–759, doi: 10.1016/j.rec.2019.03.019, indexed in Pubmed: 31405794.
16. Delluc A, Wang TF, Yap ES, et al. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: Guidance from the SSC of the ISTH. J Thromb Haemost. 2019; 17(8): 1247–1252, doi: 10.1111/jth.14478, indexed in Pubmed: 31207027.
17. Falanga A, Leader A, Ambaglio C, et al. EHA Guidelines on management of antithrombotic treatments in thrombocytopenic patients with cancer. Hemasphere. 2022; 6(8): e750, doi: 10.1097/HS9.0000000000000750, indexed in Pubmed: 35924068.
18. Byrd JC, O'Brien S, James DF, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013; 369(1): 32–42, doi: 10.1056/NEJMoa1215637, indexed in Pubmed: 23782158.

19. Byrd JC, Brown JR, O'Brien S, et al. RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014; 371(3): 213–223, doi: 10.1056/NEJMoa1400376, indexed in Pubmed: 24881631.
20. 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): 2497–2506, doi: 10.1182/blood-2014-10-606038, indexed in Pubmed: 25700432.
21. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015; 126(6): 739–745, doi: 10.1182/blood-2015-03-635326, indexed in Pubmed: 26059948.
22. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood. 2014; 124(26): 3991–3995, doi: 10.1182/blood-2014-06-583294, indexed in Pubmed: 25305202.
23. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015; 126(6): 739–745, doi: 10.1182/blood-2015-03-635326, indexed in Pubmed: 26059948.
24. Moreno C, Byrd JC, Hillmen P. Ibrutinib in previously treated chronic lymphocytic leukemia: updated efficacy and safety of the resonate study with up to four years of follow-up. Haematologica. 2017; 102(8): 311.
25. Yun S, Vincelette ND, Acharya U, et al. Risk of atrial fibrillation and bleeding diathesis associated with ibrutinib treatment: a systematic review and pooled analysis of four randomized controlled trials. Clin Lymphoma Myeloma Leuk. 2017; 17(1): 31–37.e13, doi: 10.1016/j.clml.2016.09.010, indexed in Pubmed: 27780690.
26. Gifkins DM, Matcho A, Yang H, et al. Incidence of major hemorrhage among CLL and MCL patients compared to the general elderly population: an analysis of the US SEER-Medicare Linked Database. Blood. 2015; 126(23): 3268–3268, doi: 10.1182/blood.v126.23.3268.3268.
27. Jones JA, Hillmen P, Coutre S, et al. Use of anticoagulants and antiplatelet in patients with chronic lymphocytic leukaemia treated with single-agent ibrutinib. Br J Haematol. 2017; 178(2): 286–291, doi: 10.1111/bjh.14660, indexed in Pubmed: 28397242.
28. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017; 102(10): 1796–1805, doi: 10.3324/haematol.2017.171041, indexed in Pubmed: 28751558.
29. Gribben JG, Bosch F, Cymbalista F, et al. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. Br J Haematol. 2018; 180(5): 666–679, doi: 10.1111/bjh.15080, indexed in Pubmed: 29318593.
30. Mulligan SP, Ward CM, Whalley D, et al. Atrial fibrillation, anticoagulant stroke prophylaxis and bleeding risk with ibrutinib therapy for chronic lymphocytic leukaemia and lymphoproliferative disorders. Br J Haematol. 2016; 175(3): 359–364, doi: 10.1111/bjh.14321, indexed in Pubmed: 27611114.
31. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013; 369(1): 32–42, doi: 10.1056/NEJMoa1215637, indexed in Pubmed: 23782158.
32. Burger JA, Tedeschi A, Barr PM, et al. RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015; 373(25): 2425–2437, doi: 10.1056/NEJMoa1509388, indexed in Pubmed: 26639149.
33. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol. 2016; 17(1): 48–56, doi: 10.1016/S1470-2045(15)00438-6, indexed in Pubmed: 26640039.
34. Kirchhof P, Benussi S, Kotecha D, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
35. Chai KLi, Rowan G, Seymour JF, et al. Practical recommendations for the choice of anticoagulants in the management of patients with atrial fibrillation on ibrutinib. Leuk Lymphoma. 2017; 58(12): 2811–2814, doi: 10.1080/10428194.2017.1315115, indexed in Pubmed: 28504030.
36. 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; 36(4): 624–632, doi: 10.1002/hon.2503, indexed in Pubmed: 29512173.
37. Lipsky AH, Lozier JN, Wiestner A, et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. Haematologica. 2015; 100(12): 1571–1578, doi: 10.3324/haematol.2015.126672, indexed in Pubmed: 26430171.
38. Shatzel JJ, Olson SR, Tao DL, et al. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017; 15(5): 835–847, doi: 10.1111/jth.13651, indexed in Pubmed: 28182323.