Emelina E. I., Gendlin G. E., Nikitin I. G.
Pirogov Russian National Research Medical University, Moscow, Russia

5-YEAR STUDY OF THE EFFECT OF CARDIAC MONITORING ON THE OVERALL SURVIVAL OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA RECEIVING TARGETED THERAPY WITH IBRUTINIB

Aim To evaluate the effect of cardiac monitoring on overall survival of patients with chronic lymphoid leukosis (CLL) on targeted therapy with ibrutinib.

Material and methods Survival of oncological patients depends not only on the efficacy of the antitumor therapy. Cardiovascular comorbidities and emerging cardiotoxicity of the antitumor treatment can considerably impair the quality and duration of patients' life. The problem of the need for regular cardiological monitoring of oncological patients remains unsolved. A prospective 5-year study was performed that included cardiological monitoring of patients with CLL on chronic targeted therapy with ibrutinib, the side effects of which include atrial fibrillation (AF) and arterial hypertension (AH). The study included 217 patients aged 66.0 [32.0; 910.] years; 144 of them were men aged 66.0 [32.0; 91.0] years and 83 were women aged 65.0 [39.0; 83.0] years. Electrocardiography and echocardiography, evaluation of comorbidity with the Charlson's index, and evaluation of frailty with the Geriatric 8 questionnaire and the Groningen Frailty Index were performed repeatedly for all patients. In the active cardiac monitoring group (n=89), besides the standard evaluation, active medical monitoring of symptoms and general well-being, blood pressure (BP) and pulse rate, monitoring of cardioprotective drug intake and correction, if necessary, and calling patients for examination and additional evaluation were performed every week. The remaining 128 patients were evaluated repeatedly but did not maintain the remote monitoring with messengers; they constituted a standard follow-up group.

Results This was a study of overall survival of patients with CLL on targeted therapy with ibrutinib depending on the cardiac monitoring program. The age of patients did not differ in the active cardiac monitoring group and the standard follow-up group (66.0 [60.0; 70.0] and 66.0 [59.0; 74.0] years, respectively). The active cardiac monitoring group contained somewhat more men than the standard follow-up group (68.8 and 53.9%, respectively; p=0.026). At baseline, the groups did not differ in the number of pretreatment lines, frailty test results (Geriatric 8 questionnaire, Groningen Frailty Index), comorbidity (Charlson's index), and echocardiographic data. The active cardiac monitoring group contained more patients with AH (p<0.0001), with AF (p<0.0001), patients receiving anticoagulants (p<0.0001), and a comparable number of patients with ischemic heart disease. In the active cardiac monitoring group, 70 (90.9%) of 77 patients with CLL and AH achieved goal BP whereas in the standard follow-up group, 26 (39.9%) of 66 (p<0.0001) patients achieved the BP goal, regardless of whether their elevated BP developed before or during the ibrutinib treatment. This group contained significantly more patients who required cardiac surgical intervention (coronary stenting, pacemaker implantation), 12 vs. 0 in the standard follow-up group (p=0.0004). The overall 5-year survival was significantly higher for patients of the active cardiac monitoring group, both for men (p<0.0001) and women (p<0.0001) with CLL, including patients older than 70 years (p=0.0004), CLL patients with a median pretreatment line number of 1 (p<0.0001), patients with a median chemotherapy line number of 4 (p<0.0001), and patients with genetic abnormalities (p=0.004) pretreated with fludarabine and/or anthracyclines (p<0.0001). The Cox regression analysis showed that the strongest predictor of survival was the achievement of stable goal BP in CLL patients with AH during the continuous cardiac monitoring. Despite more pronounced cardiac comorbidity, CLL patients on the active cardiac monitoring group showed a longer survival than patients on the standard follow-up. Thus, mean survival time of deceased CLL patients who had been on the cardiac monitoring was 36.1 months vs. 17.5 months (p<0.0001) for patients who had been on the standard follow-up.

Conclusion The study has demonstrated the prognostic significance of continuous participation of a cardiologist in managing onco-hematological patients. CLL patients on the active cardiac monitoring, the regular pattern of which was provided by the remote control, had a significantly higher overall survival compared to patients who visited a cardiologist periodically. A significant predomination of patients with CLL and AH who achieved stable goal BP, continuous monitoring of anticoagulant dosing in patients with AF in that group, and early detection and correction of cardiovascular complications can explain the highly significant difference in the 5-year survival between CLL patients on chronic targeted ibrutinib treatment with different cardiac monitoring programs (p<0.0001). The active cardiac monitoring with remote control allows achievement of a higher 5-year overall survival of CLL patients receiving ibrutinib (p<0.0001).

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1882

Keywords Cardio-oncology; cardiac monitoring of oncological patients; antitumor treatment; survival of oncological patients; ibrutinib

For citations Emelina E. I., Gendlin G. E., Nikitin I. G. 5-year study of the effect of cardiac monitoring on the overall survival of patients with chronic lymphocytic leukemia receiving targeted therapy with ibrutinib. Kardiologiia. 2022;62(4):20–29. [Russian: Емелина Е. И., Гендлин Г. Е., Никитин И. Г. Пятилетнее исследование влияния кардиомониторинга на общую выживаемость больных хроническим лимфолейкозом, получающих таргетную терапию ибрутинибом. Кардиология. 2022;62(4):20–29]

Corresponding author Emelina E. I. E-mail: eei1210@mail.ru

Introduction

One of the most important tasks of contemporary anti-tumor therapy is connected with the aim of increasing the life expectancy of cancer patients. As a result, new anti-tumor treatments are actively developed, including targeted drugs, immune checkpoint inhibitors and proteasome inhibitors.

The treatment outcomes and possibility of providing the selected anti-tumor regimen depend on numerous factors, including the stability of compensation of the patient's condition, which is determined by comorbidities and the toxic effects of anti-tumor therapy [1].

In Russia, the involvement of cardiologists in the anti-tumor treatment of cancer patients has for many years been the result of the personal initiative of cardiologists specializing in cardio-oncology. Regular examination of the cardiovascular system, which should be started before ordering anti-tumor treatment, remains an issue, as does the arrangement of regular cardiological follow-up of a cancer patient by a cardiologist during and following anti-tumor therapy [2–4].

Targeted therapy has been increasingly used in recent years to treat several types of cancer. It has become a breakthrough in treating many patients, including patients with chronic lymphocytic leukemia (CLL). The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, which was approved in 2016, is highly effective in patients with CLL and patients with mantle cell lymphoma, Waldenström macroglobulinemia, and marginal zone lymphoma [5, 6].

At the same time, any new anti-tumor drug not only improves the treatment of cancer patients, but also inevitably involves problems of adverse side-effects. The majority of anti-tumor agents used in clinical practice are known to invoke frequent adverse effects that can develop during their administration [7].

Targeted therapy with ibrutinib is complicated by the cardiotoxic effects, including most notably the ability to provoke atrial fibrillation (AF) and arterial hypertension (AH) [8, 9]. The clinical administration of targeted therapy with ibrutinib has been associated with other, less frequent, yet rather serious cardiovascular complications, which also challenge the logic of continuing anti-tumor therapy [10, 11].

According to a recent retrospective report on the use of ibrutinib, 42% of patients with first-time recurrence of CLL discontinued treatment, including almost 50% due to toxicity, with a median treatment duration of 6 months. The most common causes were AF, infections, pneumonitis, hemorrhage, and arthralgia [12].

Moreover, the incidence of death due to heart failure was three times higher in 21% of patients taking ibrutinib than patients receiving other treatments ($p<0.0001$). Conduction disorders, such as high-grade atrioventricular block, were identified as a new complication occurring during ibrutinib therapy, having an 18% mortality rate ($p<0.0001$) [13].

In our study, cardiac monitoring of patients receiving ibrutinib was required in the first place because of its ability to cause AF, since the concomitant use of an anticoagulant and targeted therapy with ibrutinib is associated with several challenging issues. For example, hemorrhagic events, which are likely to develop in patients with CLL, complicate the use of anticoagulant therapy (ACT). Hemorrhages can occur spontaneously in patients with CLL, including those with normal platelet counts. Patients with CLL are likely to experience high platelet variability and a tendency to thrombocytopenia. Moreover, thrombocytopathy is an adverse effect of ibrutinib, which also increases the risk of hemorrhagic events in the case of lifetime daily use of targeted therapy with ibrutinib. The need for concomitant use of ibrutinib with ACT in patients having emerging AF has been noted as of great concern [14].

Due to oncohematological concerns about patients who had a history of AF and received ACT, it was not planned to administer ibrutinib to such patients. The mere fact of patient having AF, irrespective of the need for ACT, was an issue for oncohematologists when ordering targeted therapy with ibrutinib. Thus, both the onset and the history of AF challenged the anti-tumor treatment of choice [15]. Another well known cardiotoxic effect of ibrutinib is the ability to cause arterial hypertension (AH), which is also a risk factor for poor prognosis [6, 9].

Seeking to address emerging or existing cardiac problems in our patients with CLL in a timely manner, so that each such patient could receive the best available anti-tumor treatment, we performed long-term cardiac monitoring of CLL patients receiving continuous therapy with ibrutinib.

Objective

To evaluate the effect of cardiac monitoring on overall survival of CLL patients receiving targeted therapy with ibrutinib.

Material and methods

A prospective 5 year-long study initiated in 2016 included cardiac follow-up and treatment of patients with recurrent/refractory CLL, who received continuous targeted therapy with the Bruton tyrosine kinase inhibitor ibrutinib. The median follow-up period was 42 and 27 months for survivors and deceased patients, respectively.

The study included 217 patients with CLL aged 66.0 [32.0; 91.0] years, including 144 male patients aged 66.0 [32.0; 91.0] years and 83 female patients aged 65.0 [39.0; 83.0] years.

CLL patients who were supposed to have or had already received targeted therapy with ibrutinib for 6 months mainly sought advice from the hematology center of S. P. Botkin City Clinical Hospital (Moscow, Russia).

The study included all patients with CLL receiving continuous daily targeted therapy with ibrutinib (standard dose regimen of 420 mg/day), without exceptions for comorbidities, including cardiac diseases.

All patients were examined by electrocardiography and echocardiography over time using an ACUSON Sequoia 512 device, subjected to comorbidity assessment with the Charlson index and fragility screening using the Geriatric 8 (G8) questionnaire and Groningen Frailty Index (GFI), which demonstrated a significant effect on the survival of CLL patients.

Following the first visit, patients with CLL were encouraged to use instant messengers to ensure regular remote monitoring. The most important condition for such remote follow-up was a periodic scheduled – and, if necessary, unscheduled – face-to-face examination to assess the patient's clinical state.

All patients were advised to measure BP and pulse in the morning and evening every day and maintain a measurement diary. Only 89 patients who complied and contacted with us via instant messengers were included in the active cardiac monitoring group with remote follow-up. Active medical monitoring was carried out weekly – or, if necessary, daily – as follows: assessment of patient's symptoms and well-being; regular requests of BP and pulse data; correction of antihypertensive therapy; control of anticoagulant administration. The remaining 128 patients were examined under the study protocol, with advice being sought in the event of any relevant symptoms. These patients were included in the routine follow-up group (Figure 1).

The ages of patients in the active cardiac monitoring group (n=89) and routine follow-up group (n=128) did not vary, amounting to 66.0 [60.0; 70.0] years and 66.0 [59.0; 74.0] years, respectively. There were more male patients in the routine follow-up group (68.8%) than in the active cardiac monitoring group (53.9%; p=0.026). The results of cytogenetic analysis were known for 48 patients: 17p deletion in 26 patients; 13q deletion in 11 patients; other cytogenetic abnormalities in the remaining patients. The number of treatment lines preceding ibrutinib ranged from 0 to 12, with a median of 2 lines.

The obtained data were processed in the Statistica 12.0 suite. Nonparametric statistical analysis methods were used. The Mann–Whitney test was used to determine the differences between the two independent variables; the Kruskal–Wallis test with Bonferroni correction was used for multiple comparisons. The percentages were compared using Pearson's chi-square test; Fisher's exact test was used for small values. The data are expressed as the median and interquartile range or absolute and relative values. Kaplan-Meier survival curves were built to study the overall survival. The cut-off points were determined after dividing the effect of each indicator on the overall survival of patients into deciles. Multivariate Cox regression analysis was used to assess risk factors for endpoint onset in CLL patients. The differences were statistically significant with $p<0.05$.

Results

We studied the 5 year overall survival of CLL patients who received continuous targeted therapy with ibrutinib depending on a cardiac monitoring option, starting from the first visit.

There were more patients with cardiac diseases, mainly AH and AF, in the group of active cardiac monitoring with remote follow-up (Table 1).

Due to the elevated risk of cardioembolic complications according to the CHA2DS2 VASc score, a statistically significant great number of patients with CLL received direct oral anticoagulants (DOACs) in the active cardiac monitoring group: 35 (39.8%) patients versus 9 (6.5%) patients in the routine follow-up group ($p<0.0001$).

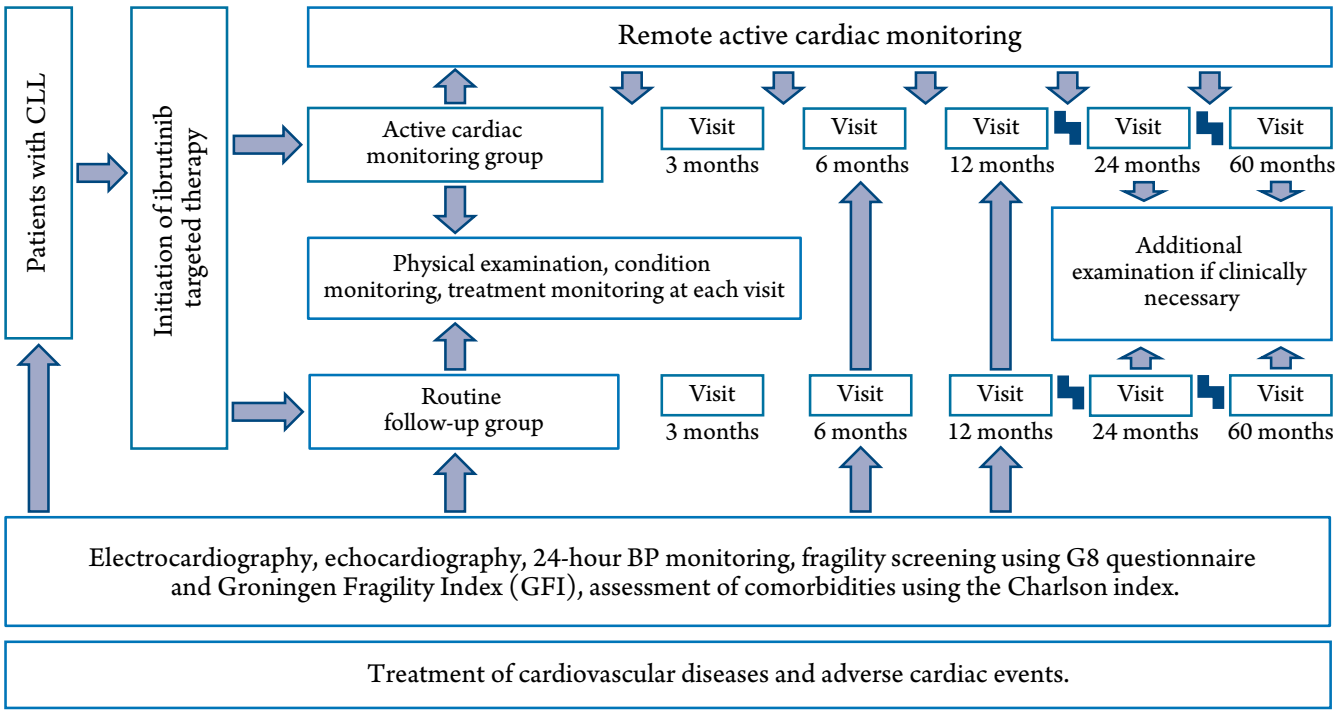
Adverse effects of ibrutinib were AF and AH in 63.2% and 18.2% of all cases, respectively. These were treated following the national clinical guidelines irrespective of whether they were diagnosed before ibrutinib was prescribed or during the anti-tumor therapy.

Due to high compliance with remote follow-up, daily measurement of BP and pulse – and, if necessary, body weight control – in the active cardiac monitoring group, we were able detect changes in patients' cardiac states in a timely manner.

The percentages of patients treated for cardiovascular disease were 87.6% in the active cardiac monitoring group and 53.6%

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1882

Figures 1. Study design



in the routine follow-up group (p<0.0001). Cardioprotective therapy included angiotensin-converting enzyme (ACE) inhibitors (perindopril and enalapril), angiotensin II receptor blockers (ARBs) (losartan), beta-blockers (bisoprolol), thiazide-like diuretics (indapamide), calcium channel blockers (amlodipine), anticoagulants (rivaroxaban, apixaban, dabigatran), antiplatelet drugs (acetylsalicylic acid and clopidogrel). Fixed combinations mainly of an ACE inhibitor and thiazide-like diuretics (perindopril and indapamide) were also used along with ARB and thiazide-like diuretics (azilsartan and chlorthalidone) in the case of AH.

In our study, prognostic significance was shown for G8, GFI, and the Charlson index, which were used to evaluate the overall survival of patients with CLL irrespective of the treatment administered. However, these indicators did not differ at baseline in the active cardiac monitoring group and other patients with CLL. Moreover, the groups did not differ in hematological status and the number of cases of second tumors (Table 2).

Echocardiographic indicators did not differ between the active cardiac monitoring group and other patients with CLL at the first visit.

Active cardiac monitoring with remote follow-up had the following important outcomes: a statistically significantly higher number of identified patients who required stenting of coronary arteries (8 patients with CLL in the active monitoring group versus the routine follow-up group; p=0.004); the implantation of an artificial pacemaker (4 patients) for sinoatrial and atrioventricular blocks; one female patient had deep vein thrombosis and pulmonary embolism (a total of patients with identified cardiovascular complications that required cardiac surgery, n=12; none in the routine follow-up group; p=0.0004); continuous monitoring of DOAC administration; timely correction to minimum doses of the administered anticoagulant considering the platelet levels and detected hemorrhagic events; replacement of one anticoagulant with another in the case of clinically significant hemorrhagic events without prejudice to the targeted therapy with ibrutinib under the increased risk of hemorrhage; thrombocytopathy; high platelet variability and liability to thrombocytopenia; achievement of the target range of BP in most patients with CLL and AH under active cardiac monitoring despite ibrutinib inducing AH. While some of our patients with CLL who received ibrutinib had a history

Table 1. Cardiac comorbidities in the active cardiac monitoring groups and patients with CLL at routine follow-up

Groups of patients with CLL	AH, n (%)	AF, n (%)	CAD, n (%)
Active cardiac monitoring (n=89)	77 (86.5)	39 (42.7)	14 (15.7)
Routine follow-up (n=128)	69 (50.7)	22 (15.9)	12 (8.7)
p	< 0.0001	< 0.0001	0.27

CLL – chronic lymphocytic leukemia; AH – arterial hypertension; AF – atrial fibrillation; CAD – coronary artery disease.

of AH, none had BP levels within the target range at the first visit despite using antihypertensive drugs. We consider that the achievement of stable target BP in 70 (90.9%) of 77 patients with CLL and AH was the most important outcome of active cardiac monitoring; the percentage of such patients was significantly lower the routine follow-up group – 26 (39.9%) of 66 patients (p<0.0001; Figure 2).

The overall survival of CLL patients with AH (n=143), who achieved (n=96) and did not achieve (n=47) the target levels of BP, differed statistically significantly (Figure 3).

The same discrepancy between the curves of overall survival depending on the achievement or non-achievement of the target BP levels was observed in all groups of patients with CLL and AH: the group of patients older than 65 years (n=83; p<0.0001); the group of patients with genetic abnormalities and AH (n=48; p=0.027). Although the survival curves diverged remarkably depending on the presence of stable target BP in the group of patients with CLL and AH with 17p deletion (n=26), this divergence did not reach statistical significance due to the small number of such patients. In the group of patients who had received potentially cardiotoxic chemotherapy with fludarabine and/or anthracyclines prior to administration of ibrutinib therapy (n=97), the achievement of stable target BP levels also caused to a significant increase in 5 year overall survival (p<0.0001). Similarly, achieving target BP levels improved overall 5 year survival in CLL patients with a median of 1 prior treatment lines (0 to 2 lines) and patients with more than 2 treatment lines (3 to 12 lines) with equal significance (p<0.0001).

The significant predominance of patients with CLL and AH in the active monitoring group who reached stable target BP levels, the continuous control of anticoagulant therapy in patients with AF in this group, as well as the early detection of cardiovascular adverse events, explain the statistically significant differences in the 5 year overall survival of CLL patients who received continuous targeted therapy with ibrutinib, depending on the cardiac monitoring option, starting from the first visit (p<0.0001).

Since the survival of male patients in our study was lower than that of female patients (p=0.005), the 5 year overall survival was estimated in the groups separately for male (Figure 4) and female patients (Figure 5) with CLL. The higher overall 5-year survival of both male and female patients with CLL who were actively monitored turned out to be statistically significant. According to the assessment of patients aged 70 years and older, the survival rate is also higher in those who were actively monitored with remote follow-up (Figure 6).

Five-year mortality in patients aged 70 years and older who were under active cardiac monitoring was also significantly lower – 20.8% versus 58.3% of patients of this age group who occasionally visit a cardiologist or a therapist (p=0.0025).

A statistically significant higher five year overall survival of patients under active cardiac monitoring was also recorded in CLL patients with genetic abnormalities who had received fludarabine and/or anthracyclines, CLL patients with the median of 1 prior treatment line, and patients with the median of 4 prior lines of chemotherapy. In this connection, it also seems worth noting that overall survival was statistically significantly affected by the use of ACE inhibitors (p=0.0005), diuretics (p=0.0034), as well as fixed combinations of an ACE inhibitor and a diuretic (p=0.004).

All data that statistically significantly affected the survival of CLL patients treated with ibrutinib were included in the Cox regression survival analysis (Table 3).

As can be seen from Table 3, the achievement of stable target levels of BP during the treatment of AH was a strong predictor of survival. Although the statistically significant regression coefficient of the factor of the treatment under active cardiac monitoring was less important, the relative risk of this predictor is low. Other indicators also demonstrate the importance of such management of patients with CLL. For example, the mean life expectancy of deceased patients treated under active cardiac monitoring was 36.1 months versus 17.5 months in the routine follow-up group (37.0 [27.0; 47.0] months (n=21) and 13.5 [6.0; 27.5] months (n=80) months, respectively; p<0.0001).

Discussion

To date, outstanding achievements have been demonstrated in the treatment of cancer patients. Drugs have been developed that can cure patients of certain malignancies or prolong remission. The Bruton tyrosine kinase inhibitor ibrutinib changed the prognosis radically in patients with CLL. High efficacy of the drug in recurrent

Table 2. Comorbidities and assessment data in CLL patient groups

Group of patients with CLL	Charlson index, score	G8 score	GFI questionnaire, score, ≥4	Second tumors, n (%)	DM, n (%)
Active cardiac monitoring (n=89)	4.0 [4.0; 5.0]	14.0 [13.0; 15.5]	27 (30.3)	12 (13.5)	17 (19.1)
Routine follow-up (n=128)	5.0 [4.0; 6.0]	14.5 [13.0; 15.5]	48 (37.5)	21 (13.5)	8 (6.3)
p	0.68	0.94	0.28	0.71	0.0035

CLL – chronic lymphocytic leukemia; Charlson index – comorbidity index;
G8 questionnaire – fragility screening using the Geriatric 8 questionnaire; GFI – Groningen Frailty Index; DM – diabetes mellitus.

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1882

ОССН

Общество Специалистов по Сердечной Недостаточности

Для профессионалов в области здравоохранения ОССН и издательство «КлинМедКонсалтинг» представляет уникальные монографии и пособия.

500 руб.*

Васюк Ю.А., Ющук Е.Н., Несветов В.В.

Монография «Кардиоонкология: новый вызов нашего времени. Сердечно-сосудистые осложнения противоопухолевого лечения»

В монографии описаны многие аспекты кардиоонкологии – важной дисциплинарной проблемы до настоящего времени остающейся малоизученной. Кардиотоксичность у онкологических пациентов является актуальной проблемой. Количество таких больных во всем мире неуклонно растет, а их активная противоопухолевая терапия, в том числе новыми, весьма агрессивными препаратами сопряжена с увеличением риска различных сердечно-сосудистых осложнений.

500 руб.*

Арутюнов Г.П., Орлова Я.А., Козиолова Н.А., Арутюнов А.Г., Драгунов Д.О., Соколова А.В.

Фундаментальные и прикладные аспекты мочегонной терапии

В данном учебном пособии описаны теоретические и прикладные аспекты мочегонной терапии. Особое внимание уделено диуретикам в лечении хронической сердечной недостаточности, артериальной гипертонии.

500 руб.*

Арутюнов Г.П.

Монография «Этюды дифференциального диагноза»

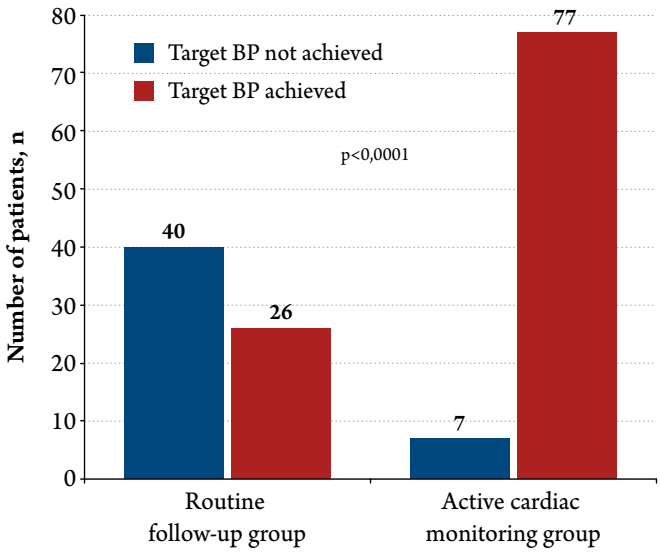
В монографии описаны навыки построения диагностической концепции на основе пропедевтического подхода к осмыслению жалоб и результатов физикального осмотра. Издание, созданное на основе личного 40-летнего опыта работы автора в многопрофильном терапевтическом стационаре будет полезно молодым специалистам, ординаторам и врачам общей практики.

Вы можете прибрести издания, обратившись в ОССН или «КлинМедКонсалтинг».

На все вопросы по заказу и доставке вам ответят по e-mail: anastasia.tarabrina@ossn.ru или по адресу 121087, г. Москва, Береговой проезд, д.5, корп. 2, 215. Тел.: +7 (495) 765 24 28.

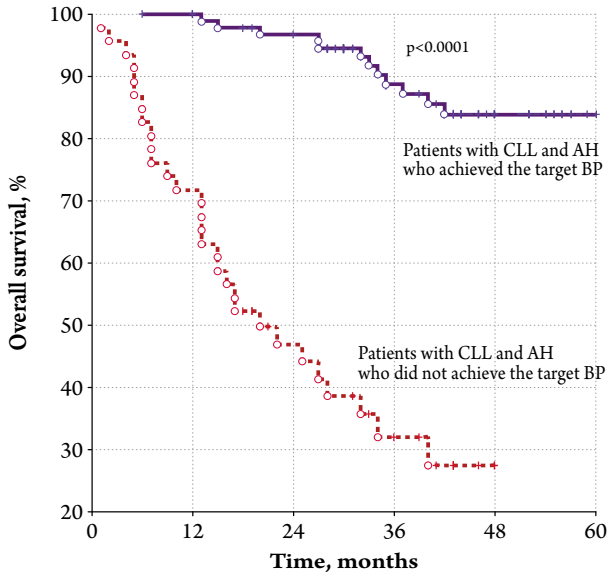
*** – стоимость почтовых услуг по пересылке оплачивается отдельно и расчитывается в зависимости от тарифов почты России или других служб доставки для каждого региона РФ.**

Figures 2. Number of patients with CLL and AH who achieved and did not achieve the target BP levels during treatment in the active cardiac monitoring and routine follow-up groups



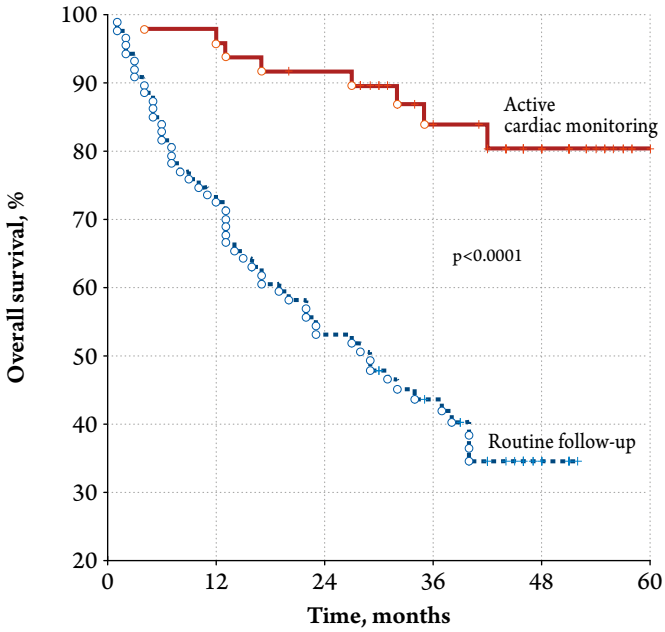
CLL – chronic lymphocytic leukemia.

Figures 3. Overall survival of patients with CLL and AH (n=143) whether the target BP level achieved (n=96) or not (n=47)



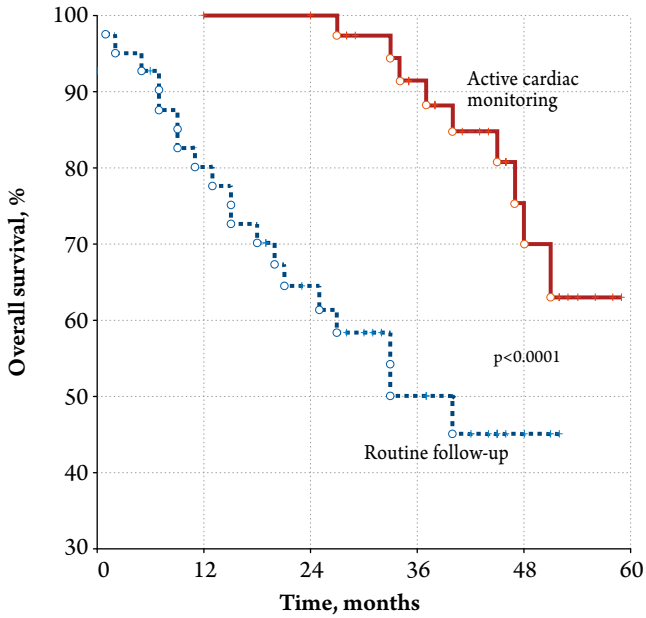
CLL – chronic lymphocytic leukemia.

Figures 4. Overall survival of male patients with CLL (n=136) who were actively monitored (n=49) or not (n=87)



CLL – chronic lymphocytic leukemia.

Figures 5. Overall survival of female patients with CLL (n=81) who were actively monitored (n=40) or followed up routinely (n=41)



CLL – chronic lymphocytic leukemia.

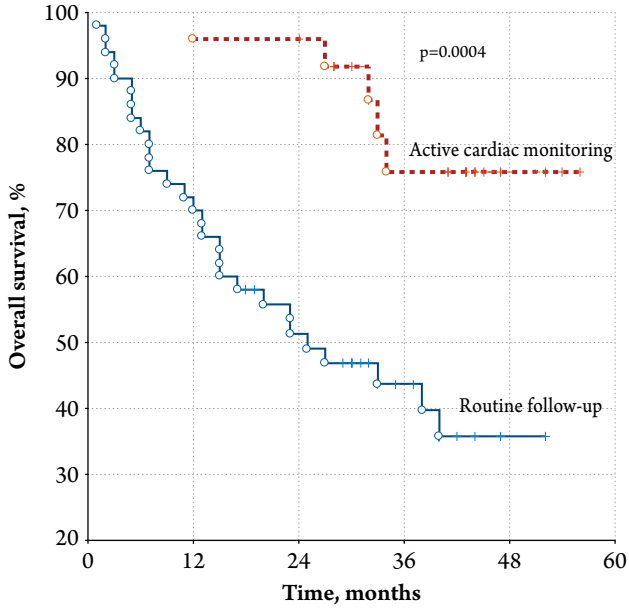
disease was demonstrated. The overall survival of CLL patients receiving ibrutinib was 87% at the median follow-up of 18 months, while the progression-free survival rate was 77% [16]. However, as in the general population, cardiovascular diseases (CVD) are the most common diseases associated with CLL, whose incidence increases due to owing to AH and AF conduction disorders induced by ibrutinib.

Thus, these patients should be continuously followed up by a cardiologist using remote techniques that have an impact on overall survival. Many studies have confirmed the special role played by cardiologists in the treatment of cancer patients [17, 18].

Patients with CLL who were under active and routine cardiac monitoring were followed up for 5 years, during which previous CVDs were actively treated; cardiac events

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1882

Figures 6. Overall survival of patients with CLL at the age of 70 years or older (n=75) who were actively monitored (n=40) or followed up routinely (n=41)



CLL – chronic lymphocytic leukemia.

occurring during the treatment with ibrutinib were detected and treated in timely manner; cardiotoxicity was identified and managed.

Patients with CLL who were under active cardiac monitoring had more severe cardiac comorbidities; the age of patients, G8 and GFI scores, Charlson index, and echocardiographic findings did not differ in the study groups.

Since patients with documented intra-vitam diagnoses of cancer who die at home are not subject to autopsy and autopsies always detect CVDs (left ventricular myocardial hypertrophy and/or dilatation, coronary atherosclerosis, etc.) characteristic of the elderly in those who died at hospital, we set out to study in overall survival in the presented groups rather than cardiac mortality; the former metric is commonly used in oncology and hematology.

As in the general population, the achievement of a stable target range of BP was determined to be the key factor for improving the prognosis in CLL patients. At the same time, the Cox regression showed that maintaining the target BP levels achieved during treatment in the active cardiac monitoring group was the strongest predictor of 5 year overall survival. Irrespective of the cause of death of CLL patients, our findings indicate that intensive treatment of combined CVDs with continuous monitoring of BP, HT, symptoms, etc., considerably and statistically significantly increases the life expectancy of such patients.

Although an increasing number of anti-cancer drugs are now used for long-term therapy, adverse events may result in canceled anti-tumor treatments or reductions in the recommended doses of a drug [1, 3, 13]. Insufficient interdisciplinary interaction between oncologists and cardiologists are often the cause of unresolved issues of cardiac comorbidities that hamper the use of a particular anti-tumor treatment [6, 8, 9].

In this work, we were able to demonstrate for the first time the importance of an active involvement of a cardiologist and active cardiac monitoring with remote follow-up in increasing the life expectancy of patients with CLL who receive anti-tumor therapy. The survival rate of patients was increased due to regular cardiac monitoring despite the presence of cancer and more severe cardiac comorbidities. Remote follow-up helped to identify minimal changes in the cardiac status and provide timely and effective interventions, including cardiac surgery, in order to achieve a stable decrease in BP to the target levels in AH. There do not appear to be any previous publications that demonstrate an increase in the 5 year overall survival of cancer patients resulting from the involvement of a cardiologist in their management.

The need to provide remote follow-up of patients has been the topic of increasing discussions. Increasingly complex automated control systems are in the process of being developed along with relevant data on the beneficial effects of such methods on the outcomes of treating patients

Table 3. Cox proportional hazards model (n=217)

Parameter	Beta (SE)	95% CI Beta		p	OR	OR 95% CI	
		lower	upper			lower	upper
Achievement of the stable target BP level	1.61 (0.33)	0.96	2.25	< 0.0001	4.98	2.61	9.51
Active cardiac monitoring	0.90 (0.33)	0.25	1.55	0.007	0.41	0.21	0.78
Antihypertensive therapy	-0.22 (0.29)	-0.78	0.34	0.59	0.80	0.48	1.41
ACE inhibitors	-0.56 (0.37)	-1.29	0.16	0.13	0.57	0.27	1.18
ARBs	-0.72 (0.55)	0.55	-1.80	0.19	0.49	0.16	1.43
Thiazide diuretics	-0.05 (0.45)	0.45	-0.93	0.91	0.95	0.39	2.29
Fixed combinations of antihyperten-sive drugs	-0.22 (0.54)	-1.29	0.85	0.69	0.80	0.28	2.33

Beta – beta regression coefficient; SE – beta standard error; 95% CI Beta – beta 95% confidence interval; OR – odds ratio; OR 95% CI – odds ratio 95% confidence interval; ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker.

with various diseases [19]. The use of available instant messengers (WhatsApp) and e-mail for remote follow-up of our patients from the active cardiac monitoring group since 2016 has resulted in regular information about the BP, HR, well-being, and symptoms of patients, helping to provide timely and effective treatment, including inviting patients for examination and additional tests where necessary.

Further studies with rigid endpoints are needed to investigate cardioprotective therapy, which is shown to affect the overall survival of cancer patients.

Conclusion

Despite cardio-oncology being well-developed in Russia, the regular cardiac follow-up of cancer patients remains a challenge. In this study, we showed for the first time that patients with chronic lymphocytic leukemia who are under regular active cardiac monitoring due to remote follow-up had a significantly higher overall survival than patients who occasionally visit a cardiologist.

Along with timely identification and correction of cardiotoxic adverse events, treatment of known cardiovascular diseases or those identified during anti-tumor therapy of cancer patients has a pronounced effect on life expectancy of patients with chronic lymphocytic leukemia receiving continuous targeted therapy with ibrutinib.

As part of the struggle to improve the survival rates of cancer patients, it is necessary to take into consideration the importance of follow-up, including a full cardiac examination of cancer patients at the stage of planning and during anti-tumor treatment. This is necessary for both course and continuous anti-tumor therapy. Active cardiac monitoring of cancer patients with remote follow-up, which has shown beneficial effects on overall survival rates, should be implemented in clinical practice.

No conflict of interest is reported.

The article was received on 18/10/2021

REFERENCES

1. Eloranta S, Smedby KE, Dickman PW, Andersson TM. Cancer survival statistics for patients and healthcare professionals – a tutorial of real-world data analysis. Journal of Internal Medicine. 2021;289(1):12–28. DOI: 10.1111/joim.13139
2. Emelina E.I., Gendlin G.E., Nikitin I.G. Cardio-oncology and Oncohematology: Examination Algorithms, Prophylactic and Treatment of Cardiotoxicity, Trends in Rehabilitation. Clinical oncohematology. 2021;14(2):239–61. [Russian: Емелина Е.И., Гендлин Г.Е., Никитин И.Г. Кардиоонкология и онкогематология: алгоритмы обследования, профилактика и лечения кардиотоксичности, направления реабилитации. Клиническая онкогематология. 2021;14(2):239-61]. DOI: 10.21320/2500-2139-2021-14-2-239-261
3. Gribben JG, Bosch F, Cymbalista F, Geisler CH, Ghia P, Hillmen P et al. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. British Journal of Haematology. 2018;180(5):666–79. DOI: 10.1111/bjh.15080
4. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Annals of Oncology. 2020;31(2):171–90. DOI: 10.1016/j.annonc.2019.10.023
5. Lee C-S, Rattu MA, Kim SS. A review of a novel, Bruton's tyrosine kinase inhibitor, ibrutinib. Journal of Oncology Pharmacy Practice. 2016;22(1):92–104. DOI: 10.1177/1078155214561281
6. Tang CPS, McMullen J, Tam C. Cardiac side effects of bruton tyrosine kinase (BTK) inhibitors. Leukemia & Lymphoma. 2018;59(7):1554–64. DOI: 10.1080/10428194.2017.1375110
7. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. European Journal of Heart Failure. 2020;22(11):1945–60. DOI: 10.1002/ejhf.1920
8. Xiao L, Salem J-E, Clauss S, Hanley A, Bapat A, Hulsmans M et al. Ibrutinib-Mediated Atrial Fibrillation Attributable to Inhibition of C-Terminal Src Kinase. Circulation. 2020;142(25):2443–55. DOI: 10.1161/CIRCULATIONAHA.120.049210
9. Dickerson T, Wiczer T, Waller A, Philippon J, Porter K, Haddad D et al. Hypertension and incident cardiovascular events following ibrutinib initiation. Blood. 2019;134(22):1919–28. DOI: 10.1182/blood.2019000840
10. Emelina E.I., Gendlin G.E., Nikitin I.G., Dmitrieva E.A., Nikitin E.A., Ptushkin V.V. Rhythm and Conduction Disorders in Patients Receiving Ibrutinib. Clinical oncohematology. 2019;12(2):120–30. [Russian: Емелина Е.И., Гендлин Г.Е., Никитин И.Г., Дмитриева Е.А., Никитин Е.А., Птушкин В.В. Нарушения ритма и проводимости у пациентов, получающих лечение ибрутинибом. Клиническая онкогематология. 2019;12(2):120-30]. DOI: 10.21320/2500-2139-2019-12-2-220-230
11. Lampson BL, Yu L, Glynn RJ, Barrientos JC, Jacobsen ED, Banerji V et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. Blood. 2017;129(18):2581–4. DOI: 10.1182/blood-2016-10-742437
12. Brown JR. How I treat CLL patients with ibrutinib. Blood. 2018;131(4):379–86. DOI: 10.1182/blood-2017-08-764712
13. Salem J-E, Manouchehri A, Bretagne M, Lebrun-Vignes B, Groarke JD, Johnson DB et al. Cardiovascular Toxicities Associated With Ibrutinib. Journal of the American College of Cardiology. 2019;74(13):1667–78. DOI: 10.1016/j.jacc.2019.07.056
14. Emelina E.I., Gendlin G.E., Nikitin I.G. Antithrombotic Therapy in Patients with Malignant Lymphoproliferative Disorders Treated with Ibrutinib. Clinical oncohematology. 2019;12(4):449–60. [Russian: Емелина Е.И., Гендлин Г.Е., Никитин И.Г. Антитромботическая терапия у пациентов со злокачественными лимфопролиферативными заболеваниями, получающих ибрутиниб. Клиническая онкогематология. 2019;12(4):449-60]. DOI: 10.21320/2500-2139-2019-12-4-449-460
15. Yun S, Vincelette ND, Acharya U, Abraham I. Risk of Atrial Fibrillation and Bleeding Diathesis Associated With Ibrutinib Treatment: A Systematic Review and Pooled Analysis of Four Randomized Controlled Trials. Clinical Lymphoma, Myeloma & Leukemia. 2017;17(1):31-37.e13. DOI: 10.1016/j.clml.2016.09.010
16. Stadnik E.A., Timofeeva N.S., Strugov V.V., Zaritskey A.Yu. Ibrutinib in the Treatment of Relapsed Chronic Lymphocytic Leukemia. Clinical oncohematology. 2018;11(1):42–9. [Russian: Стадник Е.А., Тимофеева Н.С., Стругов В.В., Зарицкий А.Ю. Ибрутиниб в лечении рецидивов хронического лимфолейкоза. Клиническая онко-

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1882

гематология. 2018;11(1):42-9]. DOI: 10.21320/2500-2139-2018-11-1-42-49
17. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S et al. Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. Circulation. 2018;137(8):e30–66. DOI: 10.1161/CIR.0000000000000556
18. Plummer C, Driessen C, Szabo Z, Mateos M-V. Management of cardiovascular risk in patients with multiple myeloma. Blood Cancer Journal. 2019;9(3):26. DOI: 10.1038/s41408-019-0183-y
19. Sukhanov M.S., Karakulova Yu.V., Prokhorov K.V., Spasenkov G.N., Koryagina N.A. Experience of remote monitoring of patients with cardiovascular diseases in the Perm Krai. Cardiovascular Therapy and Prevention. 2021;20(3):87–90. [Russian: Суханов М.С., Каракулова Ю.В., Прохоров К.В., Спасенков Г.Н., Корягина Н.А. Опыт применения удаленного мониторинга пациентов, страдающих сердечно-сосудистыми заболеваниями в Пермском крае. Кардиоваскулярная терапия и профилактика. 2021;20(3):87-90]. DOI: 10.15829/1728-8800-2021-2838