Tropical Journal of Pharmaceutical Research May 2022; 21 (5): 1117-1123
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i5.29

Original Research Article

Efficacy of imatinib mesylate in combination with radiotherapy in acute leukemia, and the effect on immune function

Mei Zhou, Liming Zhang*
Department of Hematology, Zhuji Affiliated Hospital of Shaoxing University, Shaoxing, Zhejiang Province 311800, China

For correspondence:* ***Email:* *lianzhang4194@126.com;* ***Tel:*** *+86 13777338978*

Sent for review: 1 February 2022 *Revised accepted: 28 April 2022*

Abstract

Purpose: *To evaluate the clinical efficacy of imatinib mesylate plus radiotherapy for the treatment of acute leukemia and its effect on immune function.*
Methods: *A retrospective study was conducted on 88 patients with acute leukemia admitted to Zhuji Affiliated Hospital of Shaoxing University between July 2017 and July 2021. They were assigned (randomly, 1:1) to a control group (radiotherapy) or a study group (imatinib mesylate plus radiotherapy) according to different treatment regimens. Outcome measures assessed included the clinical efficacy of the treatments in the patients and their immune functions.*
Results: *The two groups did not show any significant differences with regard to general patient profiles. After treatment, both groups presented reduced white blood cell (WBC) and platelet count (PLT) and elevated red blood cells count (RBC). The level of hemoglobin (Hb) level showed a slight decline in the control group but a significant increase in the study group ($p < 0.05$). The study group showed better improvement in the levels of WBC, PLT, RBC, and Hb than the control group ($p < 0.05$). The absolute values of peripheral blood mature neutrophils decreased in both groups after treatment, down to the lowest level at week 2, but rebounded, with higher absolute values in the study group at weeks 2, 3, and 4 of treatment ($p < 0.05$). Imatinib mesylate plus radiotherapy was associated with higher efficacy, compared with radiotherapy alone ($p < 0.05$).*
Conclusion: *Radiotherapy plus imatinib mesylate effectively enhances the immune functions of acute leukemia patients, mitigates inflammatory responses, alleviates clinical symptoms, and boosts clinical efficacy. Further clinical trials are, however, required prior to general application in clinical practice.*

Keywords: *Acute leukemia, Immune functions, Radiotherapy, Imatinib mesylate*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Acute leukemia is a malignant clonal disease of hematopoietic stem cells characterized by a high incidence and low cure rate [1]. The clinical symptoms of leukemia patients mainly include lymph node enlargement, bone pain, and hepatosplenomegaly. Some leukemia cells may also undergo extramedullary infiltration into the arachnoid membrane or adjacent neural tissues, resulting in concomitant central nervous system symptoms [2].

Currently, clinical treatment of acute leukemia primarily focuses on myelosuppression and radiotherapy in addition to general treatment measures, but the treatment efficacy is poor, and patients suffer from a high risk of recurrence. Previous research has shown that the pathogen of acute leukemia is mostly related to the BCR-ABL fusion gene, based on which the first-generation tyrosine kinase inhibitor, imatinib mesylate, was designed [3]. In 2009, the National Comprehensive Cancer Network recommended imatinib as the first-line drug in the guidelines for the treatment of acute leukemia [4].

However, the combination of imatinib mesylate and radiotherapy in treating acute leukemia has been marginally explored in China. Accordingly, the efficacy of imatinib mesylate plus radiotherapy for acute leukemia and its effect on immune function were investigated in this study.

METHODS

Patient enrolment

Patients who met the diagnostic criteria for acute leukemia in New Advances and Perspectives in Hematology [5] and the WHO Updated Classification and Diagnostic Criteria for Acute Leukemia [6], with the diagnosis confirmed by results of clinical tests, laboratory tests, immunophenotyping, and chromosomal testing; with different sites and degrees of infiltration, aged <60 years; with complete medical records and good treatment cooperation; and who were informed about the study and signed the informed consent form were recruited.

Patients with myelodysplastic syndromes; with imatinib mesylate allergy; with other serious hematological or organic diseases; with communication disorders and cognitive impairment; who did not meet the indications for radiotherapy; with discontinuation of treatment due to serious adverse reactions; with an inability to cooperate with efficacy assessment after treatment, and withdrawal of consent were excluded.

Grouping of patients

Eighty-eight leukemia patients were assigned (1:1) to receive either conventional treatment (control group) or imatinib mesylate plus radiotherapy (study group) according to different treatment protocols. The study was approved by the ethics committee of Zhuji Affiliated Hospital of Shaoxing University, and conducted as per Helsinki Declaration [7].

Treatments

Patients in both groups received symptomatic supportive treatment such as anemia treatment, infection control, bleeding control, and prevention of hyperuricemia and hyperleukocytosis.

Patients in the control group received partial spleen radiotherapy [8,9], with 6MV or 10MV of high-energy X-rays, a total therapy dose of 750-1500 cGY, and 50 cGY per dose. The radiotherapy was performed 5 times per week.

Exposure area: The radiotherapy exposure area was 1.0 cm outside the upper and left borders of the spleen, the right border was the midline of the body, and the lower border was the lower edge of the spleen or the level of the flat umbilicus. The location of the exposure area of the spleen was performed under ultrasound. A physical wedge was used to protect the kidneys and small intestine. A similar radiotherapy regimen was introduced to the patients in the study group.

The patients in the study group received 400 mg imatinib mesylate (0.4 g, Novartis Pharma Schweiz AG, approval no. H20100263) with meals daily. If the hematological response was unsatisfactory after 3 months of treatment, the dose was increased to 600 mg/day depending on the patient's condition.

Evaluation of parameters/indices

The baseline data of participants included age, BMI, disease duration, gender, disease severity, French - American-British (FAB) classification, education level, and place of residence.

Early morning fasting venous blood was collected from patients, and the white blood cell (WBC), hemoglobin (Hb), red blood cell count (RBC), and platelet count (PLT) levels were determined using a fully automated hematology analyzer. The reduction and disappearance of lymph node enlargement, hepatosplenomegaly, central nervous system symptoms, and bone pain after treatment were analyzed.

The T-Lymphocyte subsets CD4+, CD8+, and CD4+/CD8+, were determined by flow cytometry. The absolute value of peripheral blood mature neutrophils in patients was recorded for four consecutive weeks, and the percentage of mature neutrophil leukocytes in 100 nucleated cells was also counted (Richter's stain). The formulation for calculating the absolute value of

peripheral mature neutrophil leukocytes is as follows:

|peripheral mature neutrophil leukocytes| = total number of leukocytes × mature neutrophil leukocytes %

The levels of interleukin (IL)-6 and tumor necrosis factors (TNF)-α of patients were determined using an enzyme-linked immunosorbent assay according to the instructions of the Elisa kit (Beijing Bonding Company).

Clinical efficacy was determined based on the Diagnostic and Efficacy Criteria for Hematological Diseases [10]. The efficacy was considered complete response if the patients had no clinical symptoms such as infection, anemia, bleeding and cell infiltration, with a normal bone marrow profile and routine blood test results (Hb > 100g/L, WBC < 10×109 / L, PLT = (100 - 400) × 109 / L). The efficacy was considered partial response if one or two of the following conditions, namely, clinical symptoms alleviation, bone marrow profile, and routine blood test results, did not meet the criteria of complete response. The efficacy was considered ineffective if none of the following conditions, namely, the clinical symptoms alleviation, bone marrow profile, and routine blood test results, met the criteria of complete response.

Statistical analysis

All the data obtained in this study were processed using SPSS 22.0 software, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for preparation of graphs. Count data are expressed as [n (%)] and analyzed using chi-square test, and measurement data are expressed as (mean ± SD) and analyzed by Student's t-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

General patient information

The two groups (Table 1) did not show significant differences in age, BMI, disease duration, gender, disease severity, FAB classification, education, and place of residence ($p > 0.05$).

Blood profile

After treatment, both groups had reduced WBC and PLT levels and an elevated RBC level (Table 2). The level of Hb had a slight decline in the control group but a marked increase in the study group. Imatinib mesylate plus radiotherapy resulted in better outcomes in the levels of WBC, PLT, RBC, and Hb versus conventional treatment ($p < 0.05$).

Table 1: Demography of patients (n = 44)

Indicator	Control group	Study group	χ^2/t	*P*-value
Age (years)	48.97 ± 7.64	49.25 ± 7.58	0.173	0.863
BMI（kg/m^2）	23.41 ± 4.26	23.55 ± 4.37	0.152	0.879
Course of disease (months)	10.58 ± 3.55	10.67 ± 3.62	0.118	0.907
Gender			0.046	0.830
Male	24（54.55）	25（56.82）		
Female	20（45.45）	19（43.18）		
Severity of disease				
Low Risk	14（31.82）	16（36.36）	0.202	0.653
Medium Risk	27（61.36）	26（59.09）	0.047	0.828
High Risk	3（6.82）	2（4.55）	0.212	0.645
FAB classification			0.080	0.777
Acute lymphoid leukemia	8（18.18）	7（15.91）		
Acute non-lymphoid leukemia	36（81.82）	37（84.09）		
Educational level			0.210	0.647
Middle school and below	13（29.55）	15（34.09）		
High school and above	31（70.45）	29（65.91）		
Place of residence			0.202	0.653
Urban	14（31.82）	16（36.36）		
Rural	30（68.18）	28（63.64）		

Table 2: Blood profiles of patients

Index		Control group	Study group	t/P
WBC (×10^9 /L)	Before treatment	30.55 ± 8.62	30.71 ± 8.53	
	After treatment	16.07 ± 3.02	7.15 ± 2.11	16.061/<0.001
RBC (×10^{12}/L)	Before treatment	2.41 ± 0.58	2.47 ± 0.55	
	After treatment	2.89 ± 0.77	4.83 ± 0.71	12.286/<0.001
Hb (g/L)	Before treatment	120.34 ± 25.62	119.83 ± 24.93	
	After treatment	115.19 ± 18.24	130.55 ± 15.30	4.280/<0.001
PLT (×10^9/L)	Before treatment	270.82 ± 16.85	271.42 ± 17.06	
	After treatment	238.05 ± 12.41	142.52 ± 12.70	35.687/<0.001

Table 3: Extramedullary infiltration between the two groups of patients

Symptom		Control group	Study group	χ^2/*P*-value
Lymph node enlargement	Before treatment	17 (38.64)	15 (34.09)	0.1964/0.658
	After treatment (reduction)	3 (6.82)	4 (9.09)	0.379/0.538
	After treatment (disappearance)	1 (2.27)	5 (11.36)	3.942/0.047
	Improvement rate	4 (9.09)	9 (20.45)	4.394/0.036
Hepatosplenomegaly	Before treatment	26 (59.09)	25 (56.82)	0.047/0.829
	After treatment (reduction)	7 (15.91)	7 (15.91)	0.007/0.931
	After treatment (disappearance)	3 (6.82)	10 (40.91)	5.436/0.020
	Improvement rate	10 (22.73)	17 (38.64)	4.464/0.035
Bone pain	Before treatment	7 (15.91)	8 (18.18)	0.080/0.777
	After treatment (reduction)	2 (4.55)	3 (6.82)	0.134/0.714
	After treatment (disappearance)	2 (4.55)	2 (4.55)	0.024/0.876
	Improvement rate	4 (9.09)	5 (11.36)	0.045/0.833
Central nervous system symptoms	Before treatment	4 (9.09)	5 (11.36)	0.124/0.725
	After treatment (reduction)	2 (4.55)	2 (4.55)	0.090/0.764
	After treatment (disappearance)	0 (0)	0 (0)	
	Improvement rate	2 (4.55)	0 (0)	3.214/0.073

Extramedullary infiltration

Before treatment, the two groups showed similar symptoms of extramedullary infiltration (Table 3, $p > 0.05$). More patients in the study group showed reduced or resolved lymph node enlargement and hepatosplenomegaly versus the control group after treatment ($p < 0.05$).

Mature neutrophil level

The absolute values of mature neutrophils of the control group before treatment, at weeks 1, 2, 3, and 4 of treatment were 2.30 ± 1.46, 0.78 ± 0.33, 0.58 ± 0.27, 1.41 ± 0.35, and 1.80 ± 0.50, respectively, and those of the study group were 2.35±1.47, 0.80±0.31, 0.71±0.26, 1.62±0.31 and 2.15±0.58, respectively. The statistics at each timepoint were t = 2.301 and $p = 0.024$), t = 2.979 and $p = 0.004$, and t = 3.012 and $p = 0.003$, respectively. The absolute values of peripheral blood mature neutrophils (Figure 1)

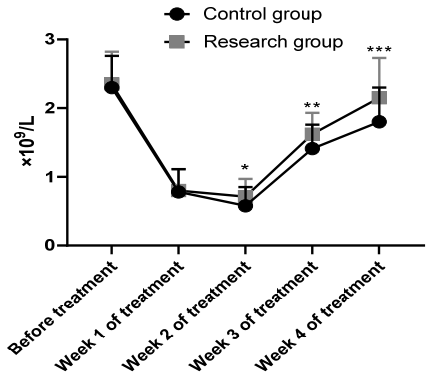

Figure 1: Comparison of the absolute values of peripheral blood mature neutrophils in the two groups of patients

Table 4: T-lymphocyte levels in the patients

Index		Control group	Study group	t/P
CD4+（%）	Before treatment	23.89 ± 5.76	23.94 ± 5.88	
	After treatment	27.06 ± 4.79	30.45 ± 6.11	2.896/0.005
CD8+（%）	Before treatment	32.33 ± 5.73	32.26 ± 5.68	
	After treatment	29.41 ± 5.72	30.30 ± 5.04	0.774/0.441
CD4+/CD8+	Before treatment	0.77 ± 0.22	0.78 ± 0.23	
	After treatment	0.91 ± 0.21	1.04 ± 0.16	3.266/0.002

Table 5: Inflammatory factor levels of the patients

Index		Control group	Study group	t/*P*-value
IL-6（ng/L）	Before treatment	303.11 ± 80.50	305.44 ± 80.26	
	After treatment	160.03 ± 77.54	105.33 ± 62.19	3.650/<0.001
TNF-α（μg/L）	Before treatment	1125.42 ± 150.33	1121.67 ± 150.89	
	After treatment	200.06 ± 70.17	149.85 ± 68.55	3.395/0.001

decreased significantly in both groups after treatment, down to the lowest level at week 2, and then rebounded, and patients receiving imatinib mesylate showed higher absolute values at weeks 2, 3, and 4 of treatment versus those receiving conventional treatment.

Immune function

The CD4+ and CD4+/CD8+ levels of patients in both groups (Table 4) were increased after treatment, with higher levels observed in the study group (p<0.05). The two groups did not differ in the CD8+ level (p > 0.05).

Therapeutic efficacy

The control group had 15 cases of complete response, 18 cases of partial response, and 11 ineffective cases. The study group had 19 cases of complete response, 21 cases of partial response, and 4 ineffective cases. The combination treatment demonstrated higher efficacy in the study group than in the control group (figure 2, X^2=3.938, p = 0.047).

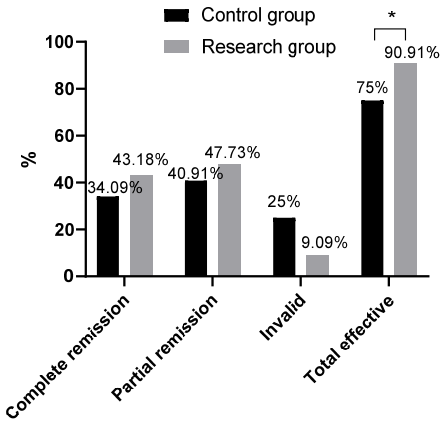

Figure 2: Comparison of the clinical efficacy of the two groups

Inflammatory response levels

The IL-6 and TNF-α levels were decreased in both groups after treatment, and the study group had lower results versus the control group (Table 5, p<0.05).

DISCUSSION

Acute leukemia is a malignant clonal disorder of hematopoietic stem cells, in which abnormal primitive and naive cells over-proliferate in the bone marrow, thereby inhibiting normal hematopoiesis and extensively infiltrating extramedullary organs such as the liver and spleen, with manifestations such as anemia, bleeding, and infection. Without effective treatment, the average survival of acute leukemia remains only about 3 months, or in severe cases, death even occurs a few days after diagnosis [11]. The main principles of current treatment for acute leukemia are to maximize the elimination of the leukemic cell population, control the proliferation of leukemic cells, and further mitigate the clinical symptoms caused by leukemic cell infiltration. Radiotherapy is a major approach for acute leukemia control. Though radiotherapy hardly achieves a cure, it suppresses the development of the disease and effectively relieves clinical symptoms, albeit with certain side effects. Autore [12] *et al*. reported that radiotherapy was effective in both slow-granulocytic spleen and granulocytosis. In addition, imatinib mesylate is preferred for the treatment of chronic granulocytic leukemia. It improves the hematological, molecular biological, and genetic indicators, with well recognized therapeutic effects. Clinical statistics show a five-year survival of 89 % among patients given imatinib mesylate.

Imatinib mesylate is a tyrosine kinase inhibitor with antitumor activity. It binds to the intracellular pocket located within the tyrosine kinase (TK), thereby inhibiting its binding to ATP and preventing phosphorylation and subsequent activation of the growth receptor and its downstream signal transduction pathways. The drug inhibits TK encoded by the bcr-abl oncogene as well as the receptor TK encoded by the c-kit and platelet-derived growth factor receptor (PDGFR) oncogene. It also inhibits the proliferation of Ph chromosome-positive hematologic malignancies and suppresses c-kit overexpression to attenuate mast cell proliferation, thereby dampening cellular behaviors mediated by PDGFR and stem cell factors in the disease [13]. Accordingly, imatinib mesylate may provide effective disease control in patients with acute leukemia and achieve disease control in synergy with radiation therapy.

Routine blood testing is the main laboratory diagnosis of acute leukemia, which is manifested by an abnormal increase in WBC and a significant decrease in hematopoietic indicators such as RBC, PLT, and Hb. In the present study, the study group had better outcomes in the levels of WBC, PLT, RBC, and Hb than the control group after treatment, which indicated the effectiveness of imatinib mesylate plus radiotherapy in improving the hematopoietic function of patients with acute leukemia, and was similar to the research results by Elsayad [14] *et al*. Their report concluded that imatinib mesylate reinforced the immune activity of normal tissues, corrected the imbalance of positive and negative regulatory factors in acute leukemia patients, inhibited the growth of leukemic cells, induced their apoptosis, alleviated the bone marrow suppression, and enhanced the hematopoietic function. Immune function impairment is a frequent symptom of acute leukemia, which relates to T-cell abnormalities.

A relevant animal experiment has revealed the immune-modulating effect of imatinib mesylate [15]. Here, the increases in CD4+ and CD4+/CD8+ levels in the study group after treatment were more significant than those in the control group, and the two groups had similar CD8+ levels before and after treatment. Moreover, the absolute values of peripheral blood mature neutrophils decreased significantly in both groups after treatment, down to the lowest level at week 2 and rebounded, with higher absolute values in the study group at weeks 2, 3, and 4 of treatment, indicating that imatinib mesylate plus radiotherapy effectively enhanced the immune function of patients.

Both IL-6 and TNF-α are critical cytokines and important inflammatory mediators involved in various physiological and immune processes. It has been reported that patients with acute leukemia exhibit abnormally elevated IL-6 and TNF-α levels, which are associated with their potential regulation effects on the proliferation and differentiation of hematopoietic stem cells and leukemic cells [16]. In the present study, the study group showed lower IL-6 and TNF-α levels versus the control group, suggesting that imatinib mesylate effectively reduced the IL-6 and TNF-α levels and regulated the proliferation and differentiation of hematopoietic stem cells and leukemic cells. Furthermore, the better treatment efficacy in the study group versus the control group in the present study suggested that imatinib mesylate plus radiotherapy effectively mitigated the clinical symptoms and enhanced the efficacy of patients with acute leukemia.

The limitations of this study lie in the small sample size and the absence of long-term efficacy investigation. Future studies with larger sample size and long-term efficacy of imatinib mesylate plus radiotherapy for acute leukemia will be conducted to provide more reliable clinical results.

CONCLUSION

Radiotherapy combined with imatinib mesylate enhances the immune function of acute leukemia patients, mitigates inflammatory levels, alleviates clinical symptoms, and boosts clinical efficacy. However, further clinical trials are required in order to ascertain its application in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

REFERENCES

1. *Lin Y, Kong F, Li H, Xu D, Jia F, Zhang X, Wang B, Li G. Comparison of target volume and clinical effects of four radiotherapy plans for acute lymphoblastic leukemia prior to hematopoietic stem cell transplantation. Mol Med Rep 2018; 18: 2762-2770.*
2. *Heath JL, Aumann WK, Maxfield CM, Wechsler DS. Isolated Central Nervous System Chloroma as a Presenting Sign of Relapsed Pediatric Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol 2018; 40: e442-e445.*
3. *Mirza AS, Lancet JE, Sweet K, Padron E, Pinilla-Ibarz J, Nardelli L, Cubitt C, List AF, Komrokji RS. A Phase II Study of CLAG Regimen Combined With Imatinib Mesylate for Relapsed or Refractory Acute Myeloid Leukemia. Clin Lymphoma Myeloma Leuk 2017; 17: 902-907.*
4. *Shimomura Y, Maruoka H, Ishikawa T. Marked response to imatinib mesylate in a patient with platelet-derived growth factor receptor beta-associated acute myeloid leukemia. Int J Hematol 2017; 105: 697-701.*
5. *Naren D, Wu J, Gong Y, Yan T, Wang K, Xu W, Yang X, Shi F, Shi R. Niemann-Pick disease type C1(NPC1) is involved in resistance against imatinib in the imatinib-resistant Ph+ acute lymphoblastic leukemia cell line SUP-B15/RI. Leuk Res 2016; 42: 59-67.*
6. *Suzuki R, Kobayashi C, Sakai A, Fukushima H, Tagawa M, Satomi K, Nanmoku T, Sumazaki R, Fukushima T. Imatinib-induced Severe Hepatitis in a 9-Year-old Girl With Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol 2015; 37: e368-71.*
7. *Associazione Medica Mondiale (AMM) dichiarazione di Helsinki. Principi etici per la ricerca medica che coinvolge soggetti umani [World Medical Association (AMM). Helsinki Declaration. Ethical principles for medical research involving human subjects]. Assist Inferm Ric 2001; 20 (2):104-7.*
8. *Agrawal R, Saha K, Mohapatra S. A rare case of imatinib mesylate induced acute kidney injury. International Journal of Basic & Clinical Pharmacology 2016; 5: 1678-1680.*
9. *Allodji RS, Tucker MA, Hawkins MM, Le Deley MC, Veres C, Weathers R, Howell R, Winter D, Haddy N, Rubino C, et al. Role of radiotherapy and chemotherapy in the risk of leukemia after childhood cancer: An international pooled analysis. Int J Cancer 2021; 148: 2079-2089.*
10. *Follin C, Svärd D, van Westen D, Björkman-Burtscher IM, Sundgren PC, Fjalldal S, Lätt J, Nilsson M, Johanson A, Erfurth EM. Microstructural white matter alterations associated to neurocognitive deficits in childhood leukemia survivors treated with cranial radiotherapy - a diffusional kurtosis study. Acta Oncol 2019; 58: 1021-1028.*
11. *Morton LM, Dores GM, Schonfeld SJ, Linet MS, Sigel BS, Lam CJK, Tucker MA, Curtis RE. Association of Chemotherapy for Solid Tumors With Development of Therapy-Related Myelodysplastic Syndrome or Acute Myeloid Leukemia in the Modern Era. JAMA Oncol 2019; 5 (3): 318-325.*
12. *Autore F, Sorà F, Chiusolo P, Annunziata M, Iurlo A, Cattaneo D, Galimberti S, Bajer JA, Sica S. 'Secondary chronic myeloid leukemia': comparison between patients previously exposed or not to chemo- and/or radiotherapy. Leuk Lymphoma 2019; 60: 3584-3586.*
13. *Hsieh CH, Tien HJ, Yu YB, Wu YH, Shueng PW, Lu YF, Wang SY, Wang LY. Simultaneous integrated boost with helical arc radiotherapy of total skin (HEARTS) to treat cutaneous manifestations of advanced, therapy-refractory cutaneous lymphoma and leukemia - dosimetry comparison of different regimens and clinical application. Radiat Oncol 2019; 14: 17.*
14. *Elsayad K, Oertel M, Haverkamp U, Eich HT. The effectiveness of radiotherapy for leukemia cutis. J Cancer Res Clin Oncol 2017; 143: 851-859.*
15. *D'Auria F, Valvano L, Rago L, Statuto T, Calice G, D'Arena G, Fusco V, Musto P. Monoclonal B-cell lymphocytosis and prostate cancer: incidence and effects of radiotherapy. J Investig Med 2019; 67: 779-782.*
16. *Karasu N, Akalin H, Gokce N, Yildirim A, Demir M, Kulak H, Celik S, Keklik M, Dundar M. Detection of mutations in CML patients resistant to tyrosine kinase inhibitor: imatinib mesylate therapy. Med Oncol 2021; 38: 120.*