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Clinical features and prognosis of duplex primary malignant neoplasms involving chronic myeloid leukemia

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Abstract

This study was to investigate clinical features and prognosis of duplex primary malignant neoplasms involving chronic myeloid leukemia (CML-DPMNs). Clinical data of thirteen CML-DPMN patients who were admitted to the First Hospital of Jilin University from May 2008 to December 2018 were collected and retrospectively analyzed. Female patients (9/13) were predominant in this cohort study. Nine patients were metachronous DPMNs (metachronous duplex primary malignant neoplasms involving chronic myeloid leukemia) with 5 years median interval time from primary malignancy to secondary malignancy. The other 4 patients were diagnosed as synchronous CML-DPMNs. Seven of the metachronous duplex primary malignant neoplasms involving chronic myeloid leukemia suffered from CML following many years of comprehensive anti-cancer therapy. Two of CML-MDPMN patients had invasive ductal carcinoma of breast after many years of treatment with imatinib. There was no difference between treatment-related CML group and non-treatment-related CML group in regard as the gender, age, white blood cell count, hemoglobin level, platelet count, and risk level. The median overall survival time of these thirteen patients with CML-DPMNs was not reached. In conclusion, female patients are more likely to suffer from the CML-DPMNs in the present article. Overall survival time of patients with DPMNs involving CML could be promising if timely and effective treatment therapy is adopted.

Abbreviations: CML = chronic myeloid leukemia, DPMNs = duplex primary malignant neoplasms, SDPMNs = synchronous duplex primary malignant neoplasms, MDPMNs = metachronous duplex primary malignant neoplasms, CML-DPMNs = duplex primary malignant neoplasms involving chronic myeloid leukemia, PM = primary malignancy, SM = secondary malignancy.

Keywords: duplex primary malignant neoplasms, chronic myeloid leukemia, synchronous multiple primary malignant neoplasms, metachronous multiple primary malignant neoplasms

1. Introduction

Multiple primary malignant neoplasms (MPMNs) refer to 2 (duplex primary malignant neoplasms [DPMNs]) or multiple primary malignant neoplasms that happen in the same patient.[1] It was first described by Billroth and Reimer in 1889 and first published in a study by Warren and Gates as early as 1932.[2,3]According to the interval period of the tumor occurrence, MPMNs is classified into synchronous MPMNs (synchronous multiple primary malignant neoplasms, the occurrence interval between 2 tumors is less than 6 months) and metachronous MPMNs (metachronous multiple primary malignant neoplasms, the occurrence interval between 2 tumors is more than 6 months).[1] Currently, more and more researchers and clinicians are paying attention to this disease. It is reported that the prevalence of MPMNs ranges from 0.52% to 11.7% in different studies and countries.[4–7] In our previous study, we found that the incidence of MPMNs was 0.99% (152/15,398) in the north of China, and there was only 1 patient that had chronic myeloid leukemia (CML) after 86 months of diagnosis of uterine choriocarcinoma.[8] Although some studies had explored clinical characteristics of DPMNs of CML patients, it still lacks systematic investigation of clinical features and prognosis of DPMNs involving CML.[8,9,10,11,12,13]

In this study, we retrospectively analyzed clinical features and prognosis of thirteen patients with DPMNs involving CML in the First Hospital of Jilin University from May 2008 to December 2018.

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Ethical approval was given by the Ethics Committee of The First Hospital of Jilin University, Changchun, China. All patients gave their written informed consent.

Consent for publication was not applicable.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

2.1. Patients

Thirteen CML-DPMN cases were retrospectively collected from clinical database of 1239 patients with newly diagnozed CML between May 2008 and December 2018 in the First Hospital of Jilin University. The incidence rate of the duplex primary malignant neoplasms involving chronic myeloid leukemia (CML-DPMNs) among the CML patients was 1.05%% (13/1239). Their clinical prognosis was evaluated throughout the patient review and/or telephone follow-up.

This study was approved by the Ethics Committee of the First Hospital of Jilin University. All identification information of the patients were deleted.

2.2. Diagnosis

CML was diagnosed based on the criteria published in 1999.[14] Polymerase chain reaction detection displayed that the thirteen CML-MPMNs patients were positive in *BCR/ABL1* fusion gene. The DPMNs were diagnosed based on the criteria proposed by Warren S and Gates O in 1932.[3] The pathological diagnosis of the secondary primary malignant neoplasm of the enrolled patients was verified by histopathological examination. Based on the concepts of synchronous multiple primary malignant neoplasms and metachronous multiple primary malignant neoplasms, the CML-DPMNs were divided into 2 types, which were named synchronous CML-DPMNs and metachronous CML-DPMNs. CML-DPMNs patients included both cases developed CML after diagnosis of another malignant tumor and cases suffered from the other malignant tumor after diagnosis of CML).

2.3. Treatments

Imatinib (400 mg/d) was used to treat CML for all CML-DPMN patients. Second generation of antineoplastic dasatinib (100 mg/day) or nilotinib (400 mg twice per day) would be used if patient was intolerant to imatinib. Other treatment strategies such as surgery, chemotherapy, radiotherapy, endocrine therapy, or comprehensive therapy were chosen for another malignant tumor according to the corresponding clinical guideline.

2.4. Overall survival

The overall survival was defined as the length of time starting from the date of a definite diagnosis of DPMNs to the last follow-up or death caused by any reason.

2.5. Risk level evaluation

Some patients received the Sokal score system, Hasford score system, and EUTOS score system risk factor evaluation.[15–17]

2.6. Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corporation, USA). Clinical efficacy was compared by using Chi-square analysis. Overall survival was analyzed by Kaplan-Meier survival analysis (log-rank). The risk factors for patients with CML-DPMSs were analyzed by Binary Logistic regression and Cox regression. Two-sided P-value $< .05$ was defined as statistically significant.

3. Results

3.1. General information

Clinical information of 1239 CML patients were reviewed from the database of the First Hospital of Jilin University between May 2008 and December 2018. Of 1239 CML patients, the ratio of male to female was 1.56:1. 82.8% (1026/1239) CML patients received tyrosine kinase inhibitors after a definite diagnosis. In this cohort study, there were thirteen patients diagnosed as DPMNs involving CML. Among them, 9 cases were metachronous duplex primary malignant neoplasms (MDPMNs), and 4 were synchronous duplex primary malignant neoplasms (SDPMNs). The ratio of female to male was 9:4. The median age of patients at diagnosis of primary malignancy (PM) was 51 years (29-68 years). The median interval time from PM to secondary malignancy (SM) of CML-MDPMN patients was 5 years (1-19 years) (Table 1).

3.2. Treatment strategy

For the CML itself, the treatment strategy for the patients with CML-MDPMN was same as that for the patients with regular CML. Of the 9 patients with CML- MDPMN involving, 7 of them suffered from CML following many years of comprehensive

Table 1

General information of thirteen patients with DPMNs involving CML.

Patient	Gender	PM	Age at diagnosis of PM	SM	Interval time from PM to SM (yr)
1	F	Uterine choriocarcinoma	29	CML	7
2	M	Adenocarcinoma(Lung)	64	CML	1
3	F	Endometrioid adenocarcinoma	56	CML	5
4	F	Invasive ductal carcinoma (breast)	35	CML	19
5	F	Invasive ductal carcinoma (breast)	41	CML	3
6	M	Squamous cell carcinoma (Lung)	68	CML	3
7	F	Endometrial cancer	51	CML	6
8	F	CML	51	Invasive ductal carcinoma (breast)	5
9	F	CML	63	Invasive ductal carcinoma (breast)	4
10	F	CML	33	Hodgkin lymphoma	0
11	M	CML	58	Gastric adenocarcinoma	0
12	F	CML	46	Invasive ductal carcinoma (breast)	0
13	M	CML	55	Squamous cell carcinoma (throat)	0

CML = chronic myeloid leukemia, F = female, M = male, PM = primary malignancy, SM = secondary malignancy.

Table 2

Treatment strategy of the thirteen CML-DPMN patients.

Treatment strategy	PM (N) (%)	SM(N) (%)
Surgery	2 (15.4)	1 (7.7)
Chemotherapy	1 (7.7)	2 (15.4)
Surgery + tamoxifen	0 (0.0)	2 (15.4)
Chemotherapy + tamoxifen	0 (0.0)	1 (7.7)
Surgery + chemotherapy	3 (23.1)	0 (0.0)
Surgery + chemotherapy + radiotherapy + tamoxifen	1 (7.7)	0 (0.0)
Imatinib	6 (46.2)	7 (53.8)
Total	13 (100)	13 (100)

CML = chronic myeloid leukemia, DPMNs = duplex primary malignant neoplasms, N = number, PM: primary malignancy; SM: secondary malignancy.

anti-cancer therapy. Among the 7 CML-MDPMN patients with solid cancer of PM, 2 of them with lung cancer developed CML with complex karyotypes after surgery, and 1 patient was intolerant to imatinib treatment because of a severe rash. Therefore, this patient was switched to nilotinib treatment. The rest 2 of the 9 CML-MDPMN patients had invasive ductal carcinoma of breast after many years of therapy with imatinib. For the treatment of the 4 synchronous duplex primary malignant neoplasms involving chronic myeloid leukemia (CML-SDPMN) patients, hydroxyurea therapy was initially adopted if white blood cell count was significantly higher than the upper normal limit, and imatinib was then administrated when white blood cell count changed to nearly average level. Meanwhile, CML-SDPMN patients underwent individual therapy for the other solid malignant tumor based on corresponding clinical guidelines at the diagnosis of SM. Specific treatment information of the thirteen CML-DPMN patients was summarized in Table 2.

3.3. Clinical features of the CMLs

According to the diagnosis order of PM and SM in patients with DPMNs, 7 patients were regarded as treatment-related CML, while the rest could be considered as non-treatment-related CML. In terms of gender, age, white blood cell count, hemoglobin level and platelet count at the time of diagnosis of CML, there were no differences between the 2 groups (Table 3). The risk level of these 2 groups was further evaluated via the Sokal score system, Hasford score system, and EUTOS score system. No difference was found between the 2 groups. Finally, Binary Logistic regression analysis and Cox regression analysis were performed to investigate possible risk factors for the patients with CML-DPMNs. However, not any risk factor was detected, which could be caused by small sample size of this study.

3.4. Overall survival

By December 2018, twelve patients with DPMNs survived. Only 1 CML patient with Hodgkin lymphoma (SDPMN) died because of CML transformation to acute myeloid leukemia. Meanwhile, following-up analysis from 538 patients with CML treated by imatinib indicated that the survival rate was 96.7% (18/538) in this group. The differences of the overall survival time of the patients in both groups (the patients with only CML versus the patients with DPMNs) were not statistically significant ($P = .191$). (Figure 1).

4. Discussion

Our data suggested that female patients with DPMNs involving CML were predominant. To illustrate the phenomenon, we systematically reviewed published articles in recent years. Helbig et al revealed that 8 of 221 CML patients developed SM after imatinib treatment with a median of 61 months, among which the ratio of female to male was 5:3.[18] Similar results were obtained from another retrospective study where 6 of the 7 CML patients with SM were female.[11] However, some studies yielded different results.[12,19] At present, some researchers considered that so many female patients suffering from DPMTs involving CML may be associated with HER2 and BRCA1/2 gene mutations.[20,21]

Although the exact mechanism of MPMNs remains uncertain, some factors, such as gene mutations, aging, chemotherapy, radiotherapy, and unhealthy lifestyle, have been verified to contribute to the development of MPMNs.[20–23] In this study, 7 patients with malignant tumor developed CML after many years of chemotherapy. We considered that chemotherapy was much likely to be the cause of the SM.

In this cohort study, there were 2 out of 6 CML patients suffered from SM after many years of imatinib therapy. Whether

Table 3

Clinical features of the CML patients with DPMNs.

Item	Treatment-related CML (n = 7)	Non-treatment-related CML (n = 6)	*P* value
Gender			1.000
Male	2	2	
Female	5	4	
Median age at diagnosis of CML (year)	57 (36-71)	53 (33-63)	.695
Median WBC count at CML (*10^9/L)	110 (16-125)	115 (18-311)	.238
Median hemoglobin level at CML (g/L)	122 (94-166)	111.5 (84-144)	.334
Median platelet count at CML (*10^9/L)	548 (204-1402)	353 (321-1547)	.780
Sokal score system			1.000
Low	2	2	
Intermediate/ high	5	4	
Hasford score system			1.000
Low	2	1	
Intermediate/high	5	5	
EUTOS score system			1.000
Low	5	5	
High	2	1	

CML = chronic myeloid leukemia, DPMNs = duplex primary malignant neoplasms, WBC = white blood cell.

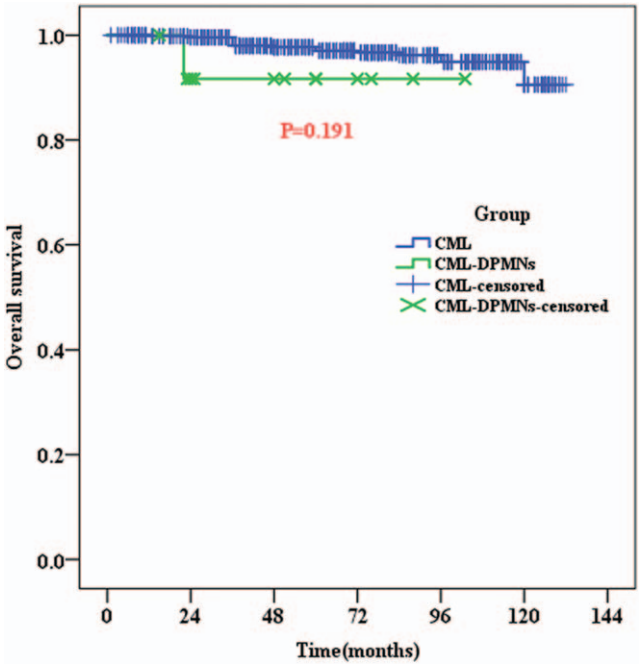

Figure 1. Overall survival of the thirteen patients with CML-DPMNs and 538 CML patients. The overall survival rate (Y axis, x 100 = percentage) and survival time (X axis) are presented in the graph. Each cut-point represents a patient. CML-DPMNs = duplex primary malignant neoplasms involving chronic myeloid leukemia.

imatinib increases the risk of SM in patients with CML or not is unclear. Several studies have explored the risk of SM in the CML patient treated by imatinib.[12,18,19,24–26] However, their conclusions are inconsistent. Therefore, other pathogenesis may exist in these DPMNs patients. This speculation was supported by the reality that 4 synchronous duplex primary malignant neoplasms involving chronic myeloid leukemia patients were diagnosed as DPMNs when they were admitted to the hospital without any chemotherapy or radiotherapy. Some scholars believe that CML itself could be a risk factor for solid cancer and hematologic tumors due to its genetic instability. Additional chromosomal abnormalities are easily detected during CML apart from chromosomal translocation of *t* (9; 22) (q34;q11), which indicates the potential of genetic instability in the patients with CML. Therefore, progenitors with genetic variability may have potential to evolve solid tumors or hematologic cancers before or after CML occurence.[27]

During the follow-up period, the survival curve of patients with CML-DPMNs reached a plateau, which indicated that the clinical prognosis of patients with CML-DPMNs was good. In this study, 91.7% of patients with CML-DPMNs underwent surgical treatment for solid tumors, and there were no recurrences of solid tumors after resection. Therefore, we considered that this good result may be closely related to these factors as follows: first, with the development of diagnostic technology, a vast majority of malignant tumors can be detected at an early stage, and malignant solid tumors can be completely removed through surgery. Second, chemotherapy, immunotherapy, radiotherapy, targeted therapy and chimeric antigen receptor T cell (CAR-T) therapies can be used to treat those patients who are unfit for surgery. These timely and appropriate treatment strategy can significantly improve overall survival time for the patients with DPMNs. This study had its limitation because it is a retrospective analysis based on a single-center with small sample size. Therefore, results from our study require further validation from a multi-center study with a larger sample size.

5. Conclusion

The vast majority of the patients with DPMNs involving CML was female. The overall survival rate of the patients with CML-DPMNs could be promising if appropriate treatment strategy were adopted.

Author contributions

CL and ZL contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

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