Types of second primary cancers influence survival in chronic lymphocytic and hairy cell leukemia patients

Guoqiao Zheng [1,2], Subhayan Chattopadhyay[1,2], Amit Sud[1,3], Kristina Sundquist[4,5,6], Jan Sundquist[4,5,6] Asta Försti[1,4], Richard Houlston[3,7], Akseli Hemminki[8,9] and Kari Hemminki [1,4]

[1] Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, D-69120, Heidelberg, Germany
[2] Faculty of Medicine, University of Heidelberg, Heidelberg, Germany
[3] Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK
[4] Center for Primary Health Care Research, Lund University, 205 02 Malmö, Sweden
[5] Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA
[6] Center for Community-based Healthcare Research and Education (CoHRE), Department of Functional Pathology, School of Medicine, Shimane University, Japan
[7] Division of Molecular Pathology, The Institute of Cancer Research, London, UK
[8] Cancer Gene Therapy Group, Faculty of Medicine, University of Helsinki, Finland
[9] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

Correspondence: Kari Hemminki, Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, Heidelberg 69120, Germany.
Telephone: +496221421800
Fax: +496221421810
Email: K.Hemminki@dkfz.de

Words: 1445 (text)

Keywords: second cancer, mortality, prognosis, survival.

Running title: Second cancer in leukemia

CONFLICTS OF INTEREST

A.H. is a shareholder in Targovax ASA. A.H. is an employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

To the Editor:

Second primary cancers (SPCs) are becoming more common as the survival in cancer is improving, and they are of main concern in cancers of good survival because they may cause early mortality. Here we want to test the hypothesis that the type of SPC is critical for survival and we further posit that the survival time can be predicted from the fatality of these cancers as first primary cancers. We test the hypotheses on two leukemias with good survival, with the common chronic lymphocytic leukemia (CLL) and the rare hairy cell leukemia (HCL). In the comparison of survival rates we use relative survival to avoid biases in the definition of the cause of death.

CLL is characterized by the gradually accumulation of small phenotypically mature malignant B lymphocytes in the blood, bone marrow and lymph nodes [1]. CLL may be preceded by monoclonal B-cell lymphocytosis, which evolves to CLL through genetic changes including somatic mutations and chromosomal aberrations [1]. Many patients are diagnosed at an asymptomatic stage and may not initially require treatment. Management of symptomatic patients includes chemotherapy with alkylating agents and purine analogues, combination of chemotherapy and immunotherapy, and drugs that target key signaling pathways [1, 2]. Survival rates for patients with CLL have continuously improved mainly due to more efficient treatment [2, 3]. Increased survival rates increase the likelihood of second primary cancers (SPCs), which may potentially interfere with survival. Elevated risks for SPC have been reported in patients with CLL, including non-melanoma skin cancer, melanoma, sarcoma, and lung, renal and prostate cancers [4, 5]. It was reported that CLL patients with second malignancies have a worse relative survival than non-CLL patients with the same second malignancies [6, 7].

HCL is a B-cell disease with common somatic *BRAF* mutations. Many patients have an indolent course and no therapies are required [8]. Therapies were developed in 1990 based on purine analogues, which achieved good response rates, and more recently targeted treatments have become available including inhibition of the mutated BRAF kinase [8]. Since 1990, relative survival

has been close to the background population among patients diagnosed before the age of 60 years and has now improved to approximately 90% even among elderly people [8]. Increased risks of SPCs in HCL patients have been reported for Hodgkin and non-Hodgkin lymphoma (NHL) and for thyroid cancer [9, 10].

We used data from the Swedish Cancer Registry to assess survival in CLL and HCL with and without SPCs. In addition, we grouped SPCs into three 'prognostic groups' based on 5-year relative survival of these cancers as first primary cancer [11, 12]: 'good survival' (relative survival >60%) included cancers in the lip, larynx, anus, breast, cervix, endometrium, prostate, testis, male genitals, kidney, bladder, melanoma, skin (squamous cell, SCC), eye, thyroid gland and endocrine and Hodgkin lymphoma; 'moderate survival' (40-60%) included cancers in the remaining upper aerodigestive tract, salivary glands, small intestine, colorectum, female genitals, bone and connective tissue and non-Hodgkin lymphoma; 'poor survival' (<40%) included cancers in the stomach, esophagus, liver, pancreas, lung, ovary and nervous system and myeloma. Relative survival was calculated by using the observed survival in the patient cohort divided by the expected survival obtained from the general cancer-free population (which can be identified using the data from the nation-wide cancer registry), matched on age, sex, calendar period, county and socioeconomic status. The expected survival was calculated with the Ederer II method [13]. The standard error of the observed survival was estimated by Greenwood's formula [14]. Patients diagnosed between 1991 and 2015 were included in the study. Relative survival in adult patients (> 20 years), with and without SPC, was measured from the time of diagnosis until death, immigration or 2015, whichever came first. Multivariable Cox proportional hazard regression model adjusting sex, age and calendar year of first cancer diagnosis and socioeconomic status was applied to assess hazard ratios (HRs) and linear trends of HRs among patients with SPC in different prognostic groups compared to patients without SPC. In this model, the diagnosis of SPC was treated as a time-dependent variable in order to avoid the immortal time bias [15]. Trend test was performed by considering patients without any SPC, with SPC of good, moderate and poor

prognosis as continuous variable. All statistical analyses were performed in SAS (version 9.4) and R software. The study was approved by the ethical committee of the University of Lund.

Among 9 338 CLL patients, a total of 1571 were diagnosed with SPC (16.8%) after a median (interquartile, 1-7) follow-up time of four years; 5 639 deaths were recorded and of these 1122 (19.9%) were in patients diagnosed with a SPC. Among 718 HCL patients, a total of 119 were diagnosed with SPC (16.6%) after a median (interquartile, 2-11) follow-up time of seven years; of 234 HCL deaths, 57 (24.4%) were recorded in patients with SPC. For CLL patients with second cancer of poor prognosis, the main two SPCs were lung and brain cancers, for those with moderate prognosis, they were non-Hodgkin lymphoma and colorectal cancer, and for those with good prognosis, they were skin (squamous cell) and prostate cancers. In HCL patients with second cancer, the main two SPCs were the same as with CLL in three groups of different prognosis. Corresponding case numbers, relative survival and 95% confidence intervals (CIs) for CLL are detailed in Supplementary Table 1.

Fig. 1 shows relative survival for CLL and HCL, with and without SPC, and in patients with SPC in the three prognostic groups. For CLL, survival was significantly better (non-overlapping 95%CIs) for patients with SPC compared to those without SPC in the first year and years 2 to 5 after diagnosis (Fig. 1a, and Supplementary Table 1). The survival rate was reversed in subsequent years but was not significant. For HCL, the data between patients with and without SPC were essentially similar: in year 1, patients with SPC had significantly better survival than those without SPC but survival was reversed at subsequent periods, yet the differences were not significant (Fig. 1b, Supplementary Table 1). CLL patients in the good prognostic group showed excellent survival during the first years but with time the rate equalized with that of moderate prognosis (Fig. 1c). In the poor prognostic group, survival was lower at all follow-up times and the rates differed significantly from patients without SPC in follow-up times after year 1. For HCL the survival of good and moderate prognosis patients did not differ but those for poor prognosis were modestly suppressed (significant for years 7 to 16 years compared to patients without SPC).

Patients had to survive some time to be diagnosed with SPC, which is a condition for immortality bias. To better understand the effect of different prognostic groups on the survival in SPC, a time dependent analysis was necessary to avoid the bias. Multivariable Cox proportional hazard regression was performed by treating SPC diagnosis as time-dependent variable stratified in prognostic groups (Table 1). CLL patients with diagnosis of SPC of good prognosis experienced worse survival compared to those without any SPC diagnosis (HR=1.76, 95%CI: 1.61-1.92). Patients with SPC of moderate (HR=2.18, 1.76-2.70) and poor prognosis (HR=5.83, 4.83-7.03) survived even worse. The trend test for HRs was highly significant (P-trend=2×10^{-16}). For HCL, the HRs for patients with SPCs of good, moderate and poor prognosis were respectively 1.69 (1.11-2.57), 2.15 (0.92, 5.02) and 13.34 (4.92-36.33) and the trends were also significant (P-trend=5×10^{-6}).

The data shows that even for cancers with relatively good overall survival, those with SPC are a subgroup for whom survival may essentially deviate from patients without SPC and who may often be forgotten in prognostic evaluations. SPCs are a challenging issue concerning cancer survival and attempts to increase patient outcome cannot disregard the effect of SPCs. We tested, for the first time, the hypothesis that survival in SPCs would follow the survival experience known for first primary cancers. The hypothesis appeared to be correct and the trend tests between prognostic groups were highly significant, especially for CLL with large case numbers. Patients with SPC presented good survival in the early stage of follow-up time which is known as immortal time but experienced poor survival after diagnosis of SPC. This pattern of survival may indicate that some active drugs have led to better outcomes early but also caused mutations that subsequently lead to second malignancies.

Early mortality in CLL and HCL may be caused by severe infections. If the patient dies, SPCs may remain underreported. Another reason for underreporting of SPCs could be less vigilant diagnostic

procedures in ill or frail patients [16]. Such underreporting may be a complication in survival studies thus masking the influence of SPCs but can be detected in the analysis of follow-up trends.

ACKNOWLEDGEMENT

We thank Patrick Reilly for excellent language editing. A.S. is the recipient of Guest Scientist Fellowship of DKFZ. Supported by the Harald Huppert Foundation, the Swedish Research Council, Deutsche Krebshilfe, Jane and Aatos Erkko Foundation, Sigrid Juselius Foundation, Finnish Cancer Organizations, ALF funding from Region Skåne, University of Helsinki and Helsinki University Central Hospital

AUTHOR CONTRIBUTIONS

Design: KH, GZ, SC

Acquisition of data: JS, KS

Statistical analysis and interpretation: GZ, SC, KH, AS, AH.

Manuscript writing: KH, RSH, GZ, SC, AS, AH, AF, KS, JS.

Approval of the final text: All authors

CONFLICTS OF INTEREST

A.H. is a shareholder in Targovax ASA. A.H. is an employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

Supplementary information is available at BCJ's website

REFERENCES

1. Kipps TJ, Stevenson FK, Wu CJ, Croce CM, Packham G, Wierda WG, *et al.* Chronic lymphocytic leukaemia. *Nature reviews Disease primers* 2017 Jan 19; **3:** 16096.

2. Kristinsson SY, Dickman PW, Wilson WH, Caporaso N, Bjorkholm M, Landgren O. Improved survival in chronic lymphocytic leukemia in the past decade: a population-based study including 11,179 patients diagnosed between 1973-2003 in Sweden. *Haematologica* 2009 Sep; **94**(9)**:** 1259-1265.

3. Pulte D, Castro FA, Jansen L, Luttmann S, Holleczek B, Nennecke A, *et al.* Trends in survival of chronic lymphocytic leukemia patients in Germany and the USA in the first decade of the twenty-first century. *Journal of hematology & oncology* 2016 Mar 22; **9:** 28.

4. Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, *et al.* Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. *J Clin Oncol* 2010 Nov 20; **28**(33)**:** 4935-4944.

5. Beiggi S, Johnston JB, Seftel MD, Pitz MW, Kumar R, Banerji V, *et al.* Increased risk of second malignancies in chronic lymphocytic leukaemia patients as compared with follicular lymphoma patients: a Canadian population-based study. *Br J Cancer* 2013 Sep 3; **109**(5)**:** 1287-1290.

6. Solomon BM, Rabe KG, Slager SL, Brewer JD, Cerhan JR, Shanafelt TD. Overall and cancer-specific survival of patients with breast, colon, kidney, and lung cancers with and without chronic lymphocytic leukemia: a SEER population-based study. *J Clin Oncol* 2013 Mar 1; **31**(7)**:** 930-937.

7. Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, *et al.* Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol* 2012 Mar 10; **30**(8)**:** 843-849.

8. Dinmohamed AG, Posthuma EFM, Visser O, Kater AP, Raymakers RAP, Doorduijn JK. Relative survival reaches a plateau in hairy cell leukemia: a population-based analysis in The Netherlands. *Blood* 2018 Mar 22; **131**(12)**:** 1380-1383.

9. Hisada M, Chen BE, Jaffe ES, Travis LB. Second cancer incidence and cause-specific mortality among 3104 patients with hairy cell leukemia: a population-based study. *J Natl Cancer Inst* 2007 Feb 7; **99**(3)**:** 215-222.

10. Cornet E, Tomowiak C, Tanguy-Schmidt A, Lepretre S, Dupuis J, Feugier P, *et al.* Long-term follow-up and second malignancies in 487 patients with hairy cell leukaemia. *Br J Haematol* 2014 Aug; **166**(3)**:** 390-400.

11. Talback M, Dickman PW. Predicting the survival of cancer patients recently diagnosed in Sweden and an evaluation of predictions published in 2004. *Acta Oncol* 2012 Jan; **51**(1)**:** 17-27.

12. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, *et al.* Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol* 2014 Jan; **15**(1)**:** 23-34.

13. Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. *Eur J Cancer* 2011 Sep; **47**(14)**:** 2202-2210.

14. Greenwood M, Topley WW. Experimental Epidemiology: Some General Considerations. *Proceedings of the Royal Society of Medicine* 1926; **19**(Sect Epidemiol State Med)**:** 31-44.

15. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983; **1**(11)**:** 710-719.

16. Chen T, Fallah M, Jansen L, Castro FA, Krilavicuite A, Katalinic A, *et al.* Distribution and risk of the second discordant primary cancers combined after a specific first primary cancer in German and Swedish cancer registries. *Cancer Lett* 2015 Dec 1; **369**(1)**:** 152-166.

FIGURE LEGEND

Fig. 1 Relative survival for CLL and HCL patients with and without SPC (a and b) and in patients with SPC in the three prognostic groups (c and d). SPC, second primary cancer, CLL, chronic lymphocytic leukemia, HCL, hairy cell leukemia

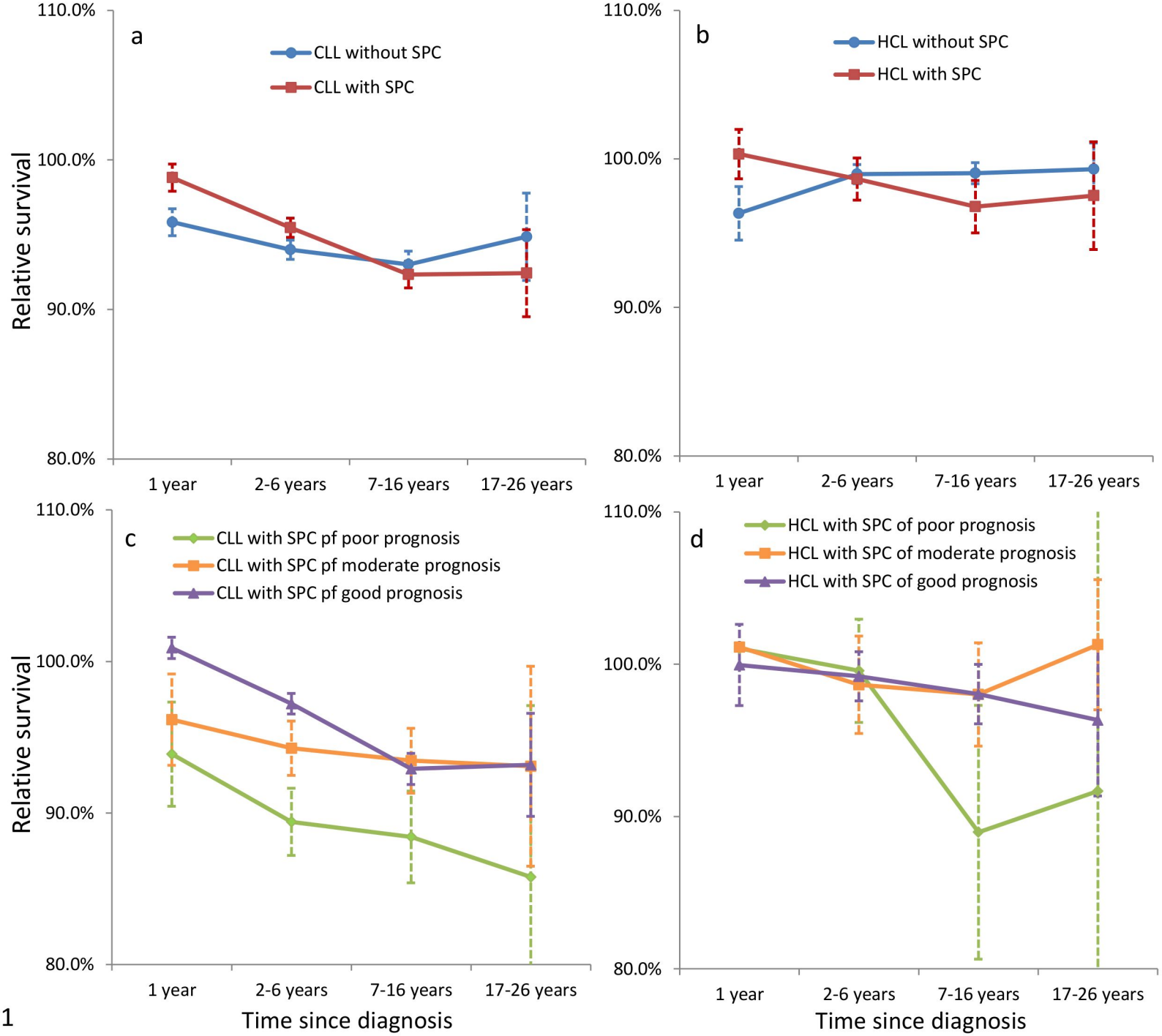
a
CLL without SPC
CLL with SPC
b
HCL without SPC
HCL with SPC
c
CLL with SPC pf poor prognosis
CLL with SPC pf moderate prognosis
CLL with SPC pf good prognosis
d
HCL with SPC of poor prognosis
HCL with SPC of moderate prognosis
HCL with SPC of good prognosis
Relative survival
110.0%
100.0%
90.0%
80.0%
1 year
2-6 years
7-16 years
17-26 years
Time since diagnosis

Figure 1

Table 1. Hazard ratio in patients diagnosed with SPC of different prognostic classes compared to those without SPC

Years since diagnosis	SPC of good prognosis		SPC of moderate prognosis		SPC of poor prognosis		P trend
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	
CLL	681	1.76 (1.61-1.92)	177	2.18 (1.76-2.70)	220	5.83 (4.83-7.03)	2×10^{-16}
HCL	31	1.69 (1.11-2.57)	11	2.15 (0.92-5.02)	9	13.34 (4.92-36.33)	5×10^{-6}

Diagnosis of second cancer of unknown primary was not considered in any prognostic groups.