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TO THE EDITOR:

Relative survival reaches a plateau in hairy cell leukemia: a population-based analysis in The Netherlands

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Around the early 1990s, the treatment of hairy cell leukemia (HCL) was revolutionized with the advent of the purine nucleoside analogs (PNAs) cladribine and pentostatin.[1,2] Earlier, in the mid-1980s, interferon α (IFN-α) was introduced for HCL management.[3] However, IFN-α responses in HCL were generally partial and short lived, as compared with PNAs that secure long-lasting complete remissions.[4-7] Although the median relapse-free survival after first-line PNA treatment has been as long as 16 years in published series,[6,8-10] it is unclear how PNA treatment impacted life expectancy of HCL patients at the population level.

At present, the few available population-based studies,[11-14] except 1 rather superficial study,[15] have examined overall survival (OS) in HCL patients. However, for diseases with an indolent course such as HCL, OS needs to be corrected for the life expectancy in the general population (ie, relative survival [RS]). Therefore, the aim of this nationwide, population-based study was to assess the contribution of primary therapy to RS among HCL patients diagnosed in the Netherlands.

We selected all HCL patients diagnosed between 1989 and 2015, with follow-up for vital statistics until February 2017, from the nationwide population-based Netherlands Cancer Registry (NCR). Details about the diagnostic criteria of HCL are provided in the supplemental Data (available on the *Blood* Web site). Information on the dates of birth and diagnosis, sex, morphology, vital statistics, and primary treatment started within 9 to 12 months after diagnosis (ie, no therapy, immunotherapy, and chemotherapy) was available for individual patients.

RS is the OS in the patient cohort divided by the expected OS of an equivalent group from the general population, matched to the patients with respect to age, sex, and calendar period.[16] Expected OS was calculated using the Ederer II method.[17] OS and RS were calculated for 3 calendar periods (1989-1993, 1994-2000, and 2001-2015) and 3 age categories (<60, 60-69, and ≥70 years), and measured from the time of diagnosis until death, emigration, or end of follow-up, whichever occurred first. Multivariable evaluation of RS using Poisson regression was performed to assess linear trends in RS over time and the relative

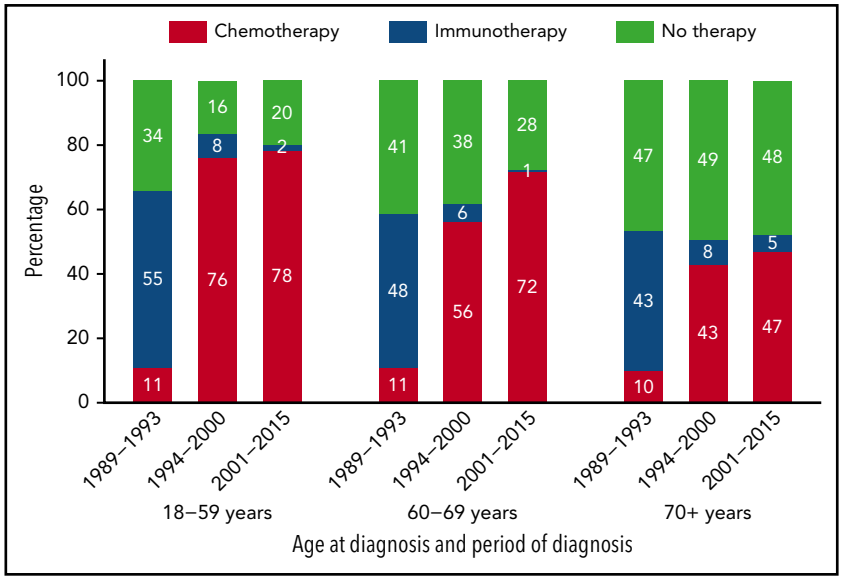
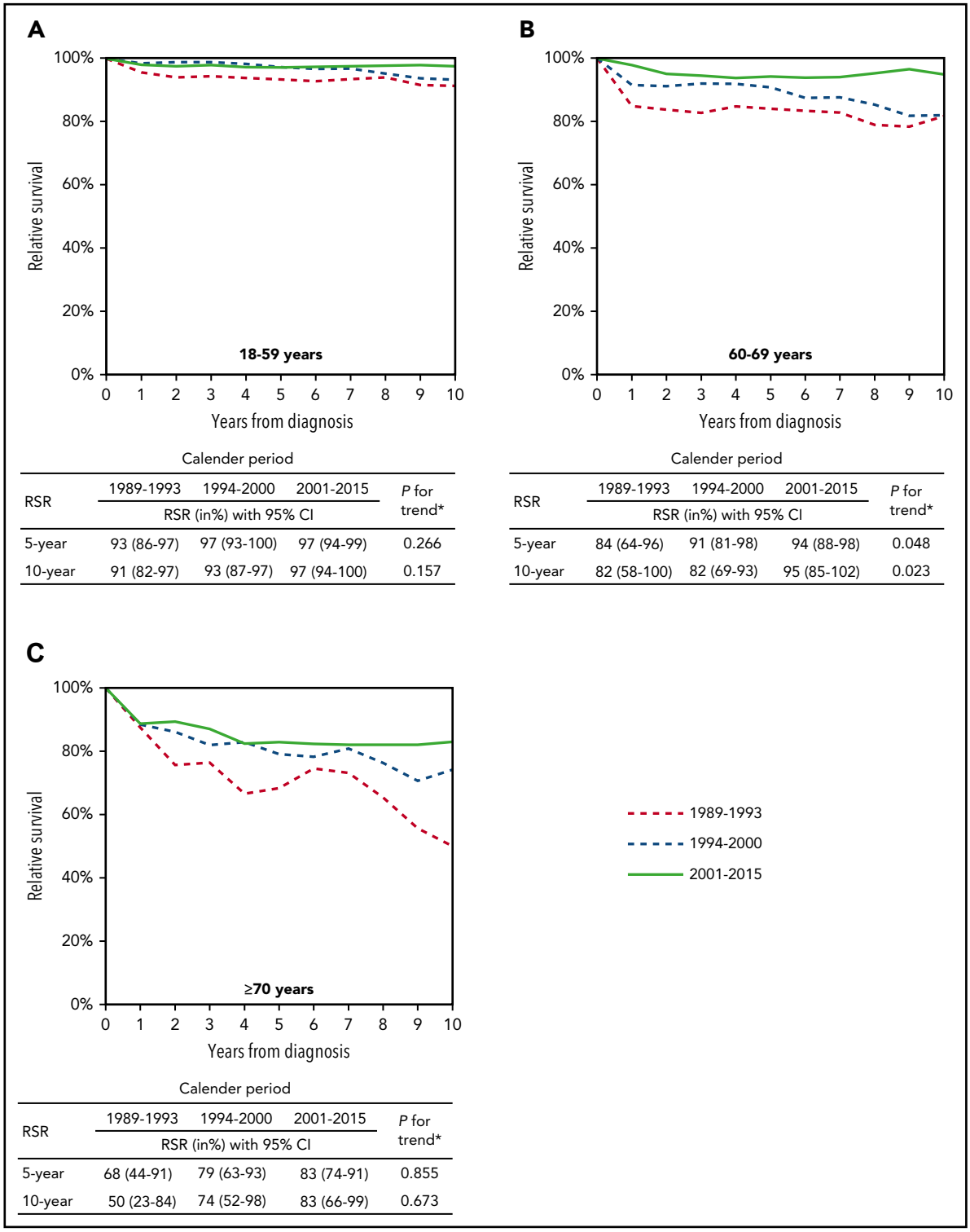


Figure 1. Primary treatment of patients with HCL in the Netherlands according age at diagnosis and calendar period of diagnosis, 1989 to 2015. The table presents the proportion of patients receiving a particular treatment within a specific calendar period and age group. The absolute number of patients within a specific calendar period and age group is shown in supplemental Table 1. Sixteen (3.7%) of the 430 patients with HCL who did not receive antineoplastic therapy underwent splenectomy. Of note, detailed data from patients diagnosed during 2014 to 2015 revealed that all PNA recipients were treated with cladribine, of whom 1 received cladribine in combination with rituximab. Further, 3 patients received rituximab monotherapy, and 1 patient received IFN-α.



Calender period

RSR	1989-1993	1994-2000	2001-2015	*P* for trend*
	RSR (in%) with 95% CI			
5-year	93 (86-97)	97 (93-100)	97 (94-99)	0.266
10-year	91 (82-97)	93 (87-97)	97 (94-100)	0.157

Calender period

RSR	1989-1993	1994-2000	2001-2015	*P* for trend*
	RSR (in%) with 95% CI			
5-year	84 (64-96)	91 (81-98)	94 (88-98)	0.048
10-year	82 (58-100)	82 (69-93)	95 (85-102)	0.023

Calender period

RSR	1989-1993	1994-2000	2001-2015	*P* for trend*
	RSR (in%) with 95% CI			
5-year	68 (44-91)	79 (63-93)	83 (74-91)	0.855
10-year	50 (23-84)	74 (52-98)	83 (66-99)	0.673

Figure 2. RS of patients with HCL in The Netherlands according to age at diagnosis and calendar period of diagnosis, 1989 to 2015. Relative survival rates (RSRs) are shown for the following age categories: <60 years (A), 60 to 69 years (B), and ≥70 years (C). The table presents the projected 5- and 10-year RSRs with 95% confidence intervals (CIs) according to age at diagnosis and calendar period of diagnosis. To illustrate the dynamics of RS, the OS in the patient cohort and the expected OS of an equivalent group from the general population, matched to the patients with respect to age, sex, and period, are plotted in supplemental Figure 2. Asterisk indicates *P* value for likelihood ratio test assessing linear trends from the period 1989 to 1993 to the period 2001 to 2015.

excess risk of mortality.[18] $P < .05$ indicated statistical significance. Further details about the statistical analyses are provided in the supplemental Data. The Privacy Review Board of the NCR approved use of anonymous data for this study.

The characteristics of 1505 HCL patients (median age, 59 years; age range, 22-95 years; 77% males) included in this study are presented in supplemental Table 1. The overall age-standardized incidence rate remained relatively stable over the 27-year study

period and was remarkably higher among males than females across all 3 age groups (supplemental Figure 1). Further, the age-specific incidence slightly increased among male patients (supplemental Figure 1A).

As shown in Figure 1, immunotherapy, most presumably IFN-α, was generally the treatment of choice in the pre-PNA era (1989-1993). Of note, information about the exact therapeutic regimen was registered in the NCR for patients diagnosed as from 2014 onward. In the era where PNAs became available in The Netherlands (1994-2000), immunotherapy was almost completely substituted by PNAs. After the year 2000, where PNAs were considered part of standard first-line therapy, the application of PNAs continued to increase, especially among patients age 60 to 69, albeit more gradually. Detailed data from patients diagnosed during 2014 to 2015 revealed that all PNA recipients were treated with cladribine.

RS improved in all age groups, with most of the improvement observed in patients age ≥60 (Figure 2). However, statistically significant improvement was restricted to patients age 60 to 69. RS reached a plateau after 2 and 4 years since diagnosis for patients age <70 and age ≥70 who were diagnosed during 2001 to 2015, respectively, without evidence of further excess mortality compared with the general population (Figure 2; supplemental Figure 2).

The primary multivariable model demonstrated an improvement of RS during the most recent calendar period (2001-2015) and a prognostic effect of age and a preexisting malignancy before HCL diagnosis (supplemental Table 2). However, after adjustment for primary therapy, the effect of calendar period lost statistical significance. This suggests that changes in the application of primary therapy accounted for the improvement during the most recent calendar period.

A novel and encouraging finding of our population-based study was that RS reached a plateau after 2 years since diagnosis among HCL patients age <70 who were diagnosed during 2001 to 2015. This indicates that the vast majority of these patients can look forward to a normal life expectancy. The low excess mortality may be directly attributed to the high complete remission rates following PNA therapy[6,19] and advances in supportive measures for infection prevention and control.[20] The current study provides a benchmark to assess late excess mortality in a contemporary era with novel strategies to manage relapse, which includes reintroduction of a PNA (with or without an anti-CD20 agent), IFN-α, splenectomy, or investigational approaches (eg, treatment with a BRAF inhibitor, ibrutinib, or immunotoxines).[20] However, seeing the excellent outcome after first-line PNA therapy in the great majority of patients,[6,19] treatment with investigational approaches such as the BRAF inhibitor vemurafenib might only benefit a specific subset of patients who are inappropriate candidates for reinduction with a PNA because of short-lived remissions, refractory disease, or an active, uncontrollable infection.[21]

Patients age ≥70 experience greater excess morality up to 4 years after diagnosis in the most recent calendar period. Several arguments can be put forward to discuss the inferior outcome among the oldest age group. First, the application of PNAs decreased with increasing age. Concomitant comorbidities at diagnosis, which were present in 69% of patients age ≥70 (supplemental Data), might affect treatment decision making in HCL, as PNAs are well known to cause severe myelosuppression. However, when these patients are solely monitored until therapy is required based on clinical symptoms, blood parameters can decline to a critical level in the absence of symptoms, which, in turn, hampers the safe application of PNA therapy in a patient population that is already vulnerable because of comorbidity. Second, during and after PNA therapy, it is inevitable that neutrophil counts further decline before recovery. Therefore, patients are placed at high risk for life-threatening infections, especially those age ≥70. Taken collectively, clinical trials are warranted that are specifically tailored to elderly, often comorbid patients with HCL who are not eligible for PNA therapy. The design of such clinical trials seems feasible, as a clinical trial was recently completed comparing ibrutinib with chlorambucil in elderly (≥65 years) patients with previously untreated chronic lymphocytic leukemia who are not eligible for fludarabine-containing chemoimmunotherapy.[22] However, it is unquestionable that international collaboration is imperative to accomplish such trials in rare diseases such as HCL.

The main strengths of our study include the use of a nationwide population-based cancer registry with comprehensive data available for individual patients. Therefore, we could directly link improvements in outcome with altering treatment practices over time. Furthermore, in contrast to clinical series, we calculated RS as a measure of disease-specific survival. At present, no study has demonstrated a plateau in HCL survival. This is explained by the fact that survival rates from current series do not correct for life expectancy in the general population.

Limitations of our study include lack of detailed clinical information throughout most of the registry (1989-2013). Therefore, inference about the specific type of chemotherapy and immunotherapy before the year 2014 remains speculative. Furthermore, the NCR captures treatment started within 9 to 12 months after diagnosis. It is fair to presume that a subset of patients who are now categorized as "no therapy" could have received therapy during the course of their disease. Finally, as discussed in the supplemental Data, the diagnostic criteria of HCL changed following the 2008 classification of the World Health Organization.[23] These changes, however, would have only marginally biased our study result, as the multivariable analyses clearly demonstrated that changes in the application of therapy accounted for the improved survival over time.

In summary, our population-based analysis supports the notion that the great majority of HCL patients in The Netherlands can look forward to a normal life expectancy in a contemporary era with well-established HCL management.

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Authorship

Contribution: A.G.D. designed the study; A.G.D. analyzed the data; O.V. collected the data; and A.G.D. wrote the manuscript with contributions from all authors, who also interpreted the data and read, commented on, and approved the final version of the manuscript.

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Footnote

The online version of this article contains a data supplement.

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TO THE EDITOR:

In vivo T-depleted reduced-intensity transplantation for *GATA2*-related immune dysfunction

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Germ line heterozygous *GATA2* mutation causes failure of mononuclear cell development, immune dysfunction, and evolution to myeloid neoplasia.[1-4] Symptoms may arise at almost any age, reaching a penetrance of 90% in the seventh decade.[3] Fatal complications include mycobacterial infection, uncontrolled herpesvirus infection, human papillomavirus (HPV)–associated