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CORRESPONDENCE

Use of Prescription Drugs in Primary Care in the Years Before and After a Malignant Hematologic Diagnosis: A Register-Based Study

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To the Editor,

Hematologic malignancies are rare diseases in primary care primarily affecting older individuals [1]. Aggressive cases, such as acute leukemia or aggressive lymphomas, often present with significant symptoms, making the diagnosis relatively apparent. Conversely, indolent hematologic malignancies may mimic more prevalent benign conditions, resulting in diagnostic delay and increasing the risk of otherwise avoidable morbidity [2, 3]. Marked changes in pre-diagnostic use of prescription drugs have previously been described in other malignant diseases [4], however, less is known of such patterns for hematologic patients. In this study, we used a nationwide exhaustive dataset to describe the use of prescription drugs in the years predating and following a diagnosis of malignant hematologic diseases to further our understanding of their early presentation, including potentially unknown patterns of early disease with the aim of improving early detection.

We collected data on prescription drug use for patients diagnosed with a malignant hematologic disease between 2008 and 2016. We reported the incidence of new prescription drug use for 3 years preceding the diagnosis and up to 2 years after the diagnosis compared to rates among age and sex-matched controls from the background population.

We included all Danish patients diagnosed with a hematologic malignancy (2008–2016) using the Danish Cancer Register (Supporting Information). Exclusion criteria were: age < 18 years, prior hematologic malignancy, and less than 3 years of Danish residency to ensure complete prescription history. Hematologic malignancies were grouped into seven categories (lymphoma, chronic lymphoid leukemia [CLL], plasma cell neoplasms, monoclonal gammopathy of undetermined significance [MGUS], myelodysplastic neoplasms [MDS], myeloproliferative neoplasms [MPN], and acute leukemia; Table S1). Five population controls were matched with each case on sex and year of birth, applying the exclusion criteria defined above.

Incident drug use was identified from the Danish National Prescription Register (for codes used, see Supporting Information) and categorized at the 4th level of the Anatomical Therapeutic Chemical Classifications System (ATC). Incident drug use was defined as the first time a patient filled a prescription for a new drug class they had not used within the preceding 3 years. Antibiotics (ATC code J) were defined as incident use of an ATC level five drug within the last month.

We calculated the incidence rate of new drug initiation in 3-month intervals from 3 years prior to 2 years after diagnosis. During the 2 years after diagnosis, subjects were censored at death and had to survive the full 3-month interval to be included in that interval. Incidence rates were reported as rates

per 100 person-months, with antibiotic and non-antibiotic drugs reported separately. Incidences were reported for the overall population and for each diagnostic subgroup. In addition, selected drug classes of clinical relevance (analgesics, anemia drugs, systemic and dermal glucocorticoids, and gout treatments, Table S2) were also presented separately. We further described the 20 specific drug classes most prevalently used in hematologic patients 6 months before and 6 months after the diagnosis, censoring at death; subjects had to survive the full 6-month interval to be counted in that interval. To test assumptions, we repeated our analyses excluding those with previous solid tumors (Table S1).

Ethical approval is not required for register-based research under Danish law.

We observed 33 715 cases of hematologic cancer (2008–2016) with lymphoma as the most frequent diagnosis. Patients with hematologic malignancies had a median age of 70 years (IQR 61–78) with a slight male preponderance (Table 1). Six-month mortality was 11.1% versus 1.4% in controls.

For controls, incident drug use was stable at ~33 new prescriptions per 100 person months. Rates among patients began rising 18 months before the diagnosis, peaking at 110 prescriptions per 100 person months (Figure 1). The increase was strongest for malignant plasma cell neoplasms (fivefold increase) and weakest for CLL (twofold increase) (Figure S1).

The use of antibiotics was elevated at the beginning of our 3-year pre-diagnostic period (Figure S2), mainly driven by patients later diagnosed with MDS and MGUS

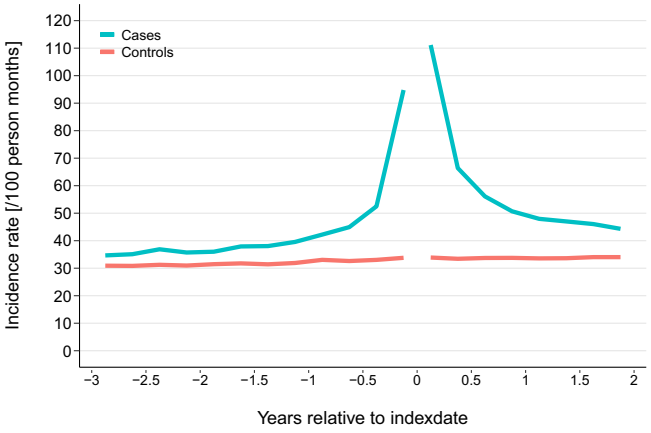

FIGURE 1 | Incident new drug use for cases compared with controls. Incident use of prescription drugs for hematologic cancer patients and their controls matched for sex and age presented as number of new prescriptions per 100 person months. Incident drug use was defined as no previous prescription for that drug class within the previous three years. Prescriptions were counted in three-month time intervals. Subjects were censored in case of death and had to be alive for the full three-month interval to be included in that interval. Index date is date of diagnosis for the case which the same date used for their corresponding population controls.

TABLE 1 | Demographics of the cases and controls.

	Cases $N = 33\,715$	Controls $N = 162\,649$
Age, years	70 [61; 78][a]	69 [60; 77]
Sex, *n* (%)		
Male	18 573 (55.1)	88 990 (54.7)
Female	15 142 (44.9)	73 659 (45.3)
Charlson Comorbidity Index, *n* (%)		
0	21 115 (62.6)	120 389 (74.0)
1	3722 (11.0)	12 912 (7.9)
2	5482 (16.3)	20 064 (12.3)
> 2	3396 (10.1)	9284 (5.7)
Hematologic malignancy sub-group, *n* (%)		
Lymphoma	10 864 (32.2)	NA
Plasma cell neoplasms	4431 (13.1)	NA
Monoclonal gammopathy of undetermined significance	4605 (13.7)	NA
Chronic lymphoid leukemia	4100 (12.2)	NA
Myeloproliferative disease	4822 (14.3)	NA
Myelodysplastic neoplasms	2792 (8.3)	NA
Acute leukemia	2101 (6.2)	NA

Note: Demographics for all patients diagnosed with a hematologic malignancy in Denmark from 2008 to 2016 and sex- and age matched population controls.
Abbreviation: NA = not applicable.
[a]Median [IQR], all such numbers.

(Figure S3). Antibiotics incidence increased further at 18 months before diagnosis, peaking at diagnosis across subgroups (Figure S3).

Among our predefined drug classes, the use of opioids, NSAIDs, systemic corticosteroids, and anemia treatments increased 6 months before diagnosis; gout treatments increased at diagnosis, while topical corticosteroids did not increase (Figure S4). Opioid use peaked at the time of diagnosis with a sixfold excess compared with controls.

Six months before diagnosis, patients had excessive prevalent use of paracetamol, tramadol, and penicillin compared with controls (Tables S3 and S4).

Sensitivity analyses excluding subjects with previous solid tumors showed similar results (data not shown).

In this descriptive study including all Danish patients diagnosed with a hematologic malignancy from 2008 to 2016, we observed an increased incidence of new prescription drug use beginning at 18 months prior to and peaking at the time of diagnosis. This was most pronounced in plasma cell neoplasms and least in CLL. Analgesics and antibiotics were the most common pre-diagnostic prescriptions among hematologic patients, reaffirming known symptoms of hematologic malignancy, while we did not identify any novel patterns of early disease.

The excess pre-diagnostic use of analgesics, particularly opioids, was mainly driven by plasma cell neoplasms. Severe pain is a known symptom of multiple myeloma, where diagnostic latency is well-described, our study confirming these patterns in a nationwide setting [5].

The use of antibiotics increased immediately before all hematologic malignancy diagnoses, most likely reflecting infectious disease prompting bloodwork that led to the diagnosis. In MDS and MGUS—but not in CLL—an increased use of antibiotics was observed years before the diagnosis, suggesting prolonged symptomatic phases consistent with prior observations of infections and blood work abnormalities in these conditions [3, 6–8] Although early treatment of for example, low-risk MDS may not improve survival, diagnostics could alter clinicians' approach to treatment and prophylaxis against infections, reducing MDS driven morbidity [9]. Furthermore, primary care physicians should remain focused on identifying underlying disease in patients with opioid-treated pain and frequent infections.

We chose to define several drug classes of interest a priori based on our clinical experience in early presentation of hematologic disease [10]. This was done to ensure we would detect any small changes in all clinically relevant prescription drugs, including those uncommonly used. We noted increased use of supplements for treating anemia (iron, B12, and folic acid) in the last 6 months pre-diagnosis, with patients having six times as many new prescriptions as controls. This likely reflects undetected hematologic malignancy causing the anemia for these patients and suggests that supplement treatment may be used empirically and delay diagnosis. Our observations suggest a need for further studies into anemia testing and handling in primary care.

Strengths of the present study include the use of the exhaustive Danish health care registers allowing for the inclusion of all Danish patients diagnosed with hematologic cancer as well as the matching of five population controls resulting in a comprehensive and uniquely unselected material. The cross-linkage of this data to the Prescription Register enables a close and extensive follow-up with a unique description of the pre-diagnostic period.

Limitations include the lack of individual-level data on hospital drugs in The Prescription Register, where drugs dispensed in the outpatient clinic or administered during hospital admission are not included in our data, likely underestimating post-diagnostic drug use (particularly antibiotics often dispensed at the outpatient clinic). The national health registers lack primary care clinical data, and while the prescription register includes drug indications, these are often made in broad terms. Thus, using prescriptions to infer underlying conditions involves some uncertainty, though likely of limited impact here, as the drugs studied are typically prescribed for well-defined indications. Prescription data was only available up to 2018, limiting inclusion of cancer cases to 2016 to allow ≥ 2 years of post-diagnostic prescription follow-up. Although this limits the study to "older" diagnoses, it also means that all cases were classified under the same 2008 World Health Organization diagnostic criteria, ensuring homogeneity of the cohort. Later diagnostic updates are unlikely to affect prescription outcomes.

In conclusion, in a thorough description of all prescription drug use 3 years pre- and 2 years post-malignant hematologic diagnoses, we did not observe drug use suggesting novel symptoms of early disease. Rather, we confirm already well-known disease patterns and demonstrate a years-long symptomatic pre-diagnostic stage for several malignancies including MDS and MGUS. To address pre-diagnostic morbidity, early detection of hematologic malignancy should remain a priority, well-known symptoms remaining important markers in models attempting to enhance risk predictions or guide interventions in the future.

Ethics Statement

An approval by the ethics committee is not required for register-based research according to Danish legislation, nor was patient consent required because patients were not approached at any time during the study. No data was reproduced from previous work by the authors or others.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The Danish national registers used for this study were administered by the Statistics Denmark. Data cannot be made publicly available as it contains personal information. However, data can be accessed through affiliation with a Danish research institution authorized for data use https://www.dst.dk/en/TilSalg/Forskningsservice and researchers can be approved for data access under the authorization of their institution.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Incident new drug use according to hematologic diagnosis. **Figure S2:** Incident new antibiotics use for cases compared with controls. **Figure S3:** Incident antibiotics use according to hematologic diagnosis. **Figure S4:** Use of predefined drug classes in cases relative to controls. **Table S1:** Hematologic diseases groups. **Table S2:** Antibiotics and predefined drugs of interest. **Table S3:** The 20 most used drug groups among hematologic patients and population controls 6 months before and 6 months after the diagnosis or index date of random sampling. **Table S4:** The 10 most used drug groups among hematologic patients 6 months before and 6 months after the diagnosis according to diagnostic subgroup.