Automated Extraction of Adverse Events Reveals Relationship Between HMA/Ven Cycle Duration and Symptom Burden

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Abstract: AML-1393

Introduction

The combination of hypothemylating agents with ventoclax (HMA/Ven) is a standard treatment for many patients with acute myeloid leukemia (AML). Although the efficacy of these regimens has been demonstrated in multiple clinician trials, during routine clinical practice these regimens require frequent dose modifications from published protocols included dose adjustments and treatment delays due to toxicity. While there is limited prospective data on efficacy for a small number of the most common treatment modifications, for most situations there is little data to guide different options for treatment modification. Real world data could provide a useful adjunct to prospective studies in addressing these questions, but it is often challenging to obtain the granularity of data requires. Leveraging recent advances in NLP and EHR databases, we have developed pipelines to extract treatment details and patient toxicities from EHR databases. We apply these tools to a single center cohort to understand how cycle duration affects treatment toxicity for HMA/Ven.

Extraction of treatment details from EHR databases

Structured EHR databases are valuable resources for real-world data analysis. However, data is often formatted in a way that makes it difficult to perform downstream analysis. For example medication data is often stored as individual administrations/orders rather than reflecting treatment details relevant to oncology such as the multi-agent treatment regimen, dose modifications and dose interruptions. We therefore developed an algorithm to match raw medication data to reference treatment protocols (HemOnc.org) and extract any treatment modifications from the reference protocol. Details of patients' treatment course are exported in json format for easy subsequent analysis.

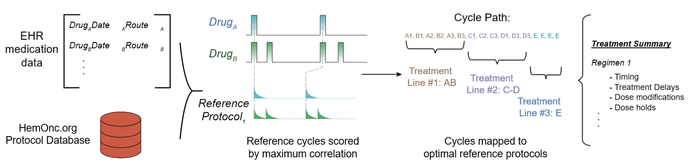

Figure #1: Automated Extraction of Treatment Details from Drug Administration Data
Schematic of algorithm to convert raw drug administration data to reference treatment protocols and identify deviations from reference treatments.

Development of LLM based Adverse Event Pipeline

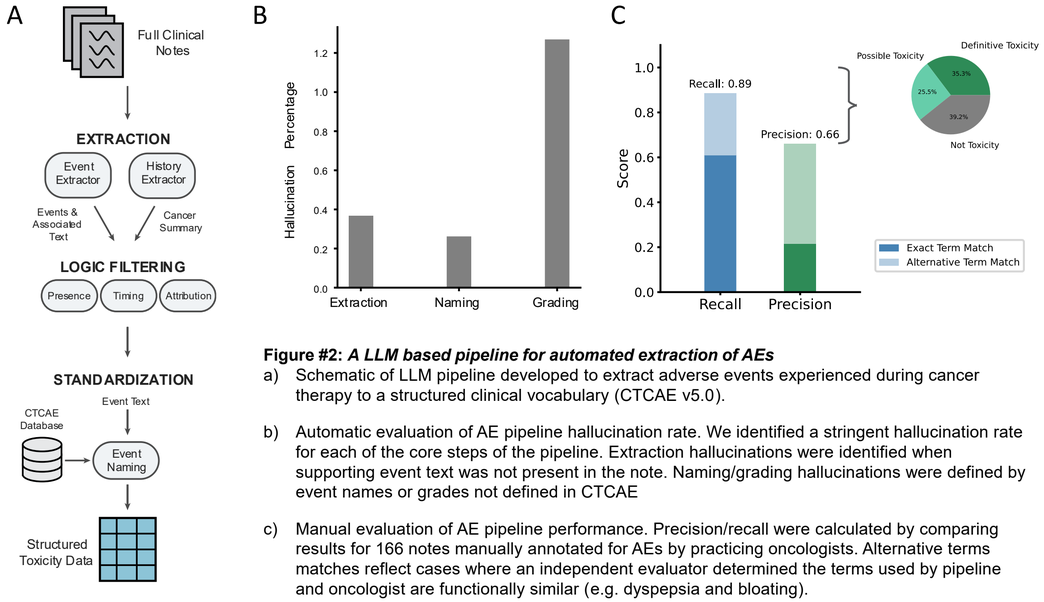

Figure #2: *A LLM based pipeline for automated extraction of AEs*

a) Schematic of LLM pipeline developed to extract adverse events experienced during cancer therapy to a structured clinical vocabulary (CTCAE v5.0).

b) Automatic evaluation of AE pipeline hallucination rate. We identified a stringent hallucination rate for each of the core steps of the pipeline. Extraction hallucinations were identified when supporting event text was not present in the note. Naming/grading hallucinations were defined by event names or grades not defined in CTCAE

c) Manual evaluation of AE pipeline performance. Precision/recall were calculated by comparing results for 166 notes manually annotated for AEs by practicing oncologists. Alternative terms matches reflect cases where an independent evaluator determined the terms used by pipeline and oncologist are functionally similar (e.g. dyspepsia and bloating).

Relationship between Cycle Duration and AE Burden in HMA/Ven

Clinical Cohort

We identified 175 patients treatment with HMA/Ven between 2017 to 2026 at a single institution (UCSF) and affiliated sites. We stratified the cohort into tertiles based on median HMA/Ven cycle length and performed all comparisons between the top and bottom tertiles. Median cycle length was 31 days in the standard duration cohort and 60 days in the extended duration cohort. Total time on therapy was modestly higher in the extended duration cohort (median 137 days vs 169 days, Wilcoxon ranksum pvalue 0.01).

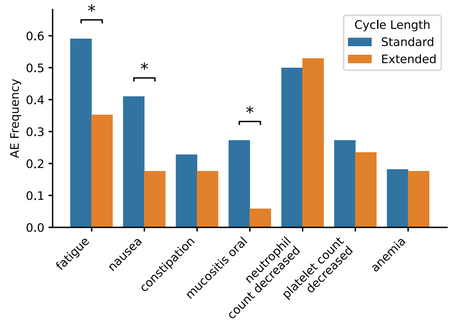

Figure #3: AE Burden by Cycle Duration
Barplot displays frequency of each AE during treatment. Significance tested by one-sided fisher exact test. FDR < 20% for bars marked with *.

Outcomes by HMA/Ven cycle duration

In addition to treatment toxicity, we also studied whether there was a difference in outcomes between the patients with standard cycle lengths and those with extended cycle lengths. We focused on ED visits (captured at the primary institution and affiliated Eds) as another hard outcome related to treatment toxicity and overall survival.

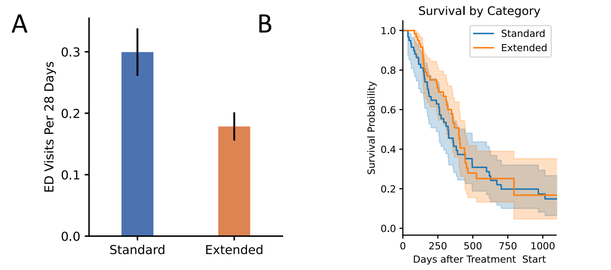

Figure #3: Treatment Outcomes Stratified by Cycle Length

a) Barplot of average number of ED visits per 28 days (+/- S.E.M) in the standard and extended cycle duration cohorts. Incident rate ratio 0.41 (50% confidence interval 0.30 – 0.55, p-value < 0.001 by poisson regression).

b) Survival curves for standard and extended cycle duration cohorts from start of treatment. Difference not significant by log-rank test.

Conclusions and Future Directions

- Expansion in the availability of EHR databases and advances in natural language procession allow for more detailed retrospective studies of how the details of treatment administration might affect patient experience.
- Treatment delays/extensions are frequent for patients on aza/ven with only 1/3 of patients able to receive cycles at the studied 28 day interval. 1/3 of patients have delays of up to 4 weeks on therapy.
- Less frequent dosing is associated with lower rates of non-hematologic toxicities including fatigue, nausea, and mucositis in an unadjusted comparison as well as lower rates of ED visits.
- Further work on the patient characteristics that lead to decreased frequency of dosing is necessary to contextualize these differences.