Frequency of Practice-Changing Findings Identified by Comprehensive Genomic Profiling in Non-Myeloid Hematologic Malignancies

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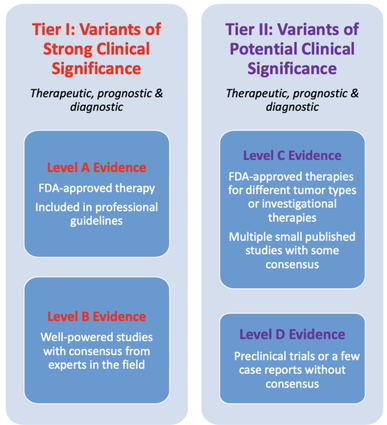
Introduction

- Comprehensive genomic profiling (CGP) is used to guide management in myeloid and advanced solid malignancies
- The role of CGP in non-myeloid hematologic malignancies is less clear
- CGP identifies potentially actionable variants, but these variants may not lead to changes in clinical practice

Our aim was to determine how often variants found on CGP of non-myeloid malignancies changed clinical practice.

Methods

- Retrospective review of 101 patients with non-myeloid hematologic malignancies at Duke who underwent CGP
- 105 samples sent for CGP by FoundationOne Heme (104) or HemeComplete (1) in 2014–2021
- Classified variants by evidence level according to AMP/ASCO/CAP guidelines:



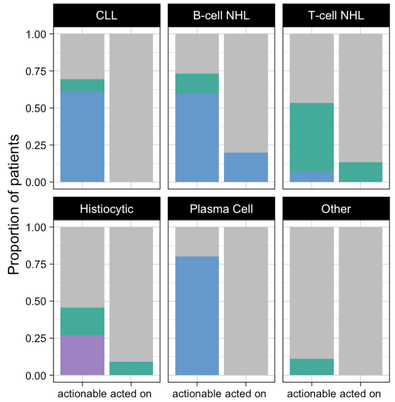
Li M.M. *et al.* Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer. *J Mol Diagn*. 2017 Jan;19(1):4-23.

- For therapy sensitizing variants, level C was divided into two separate levels:
  - C1 – clinical trial
  - C2 – approved for different tumor type

CGP often identified variants of clinical significance, but only a fraction of identified variants led to changes in therapy.

Therapy Sensitizing Variants

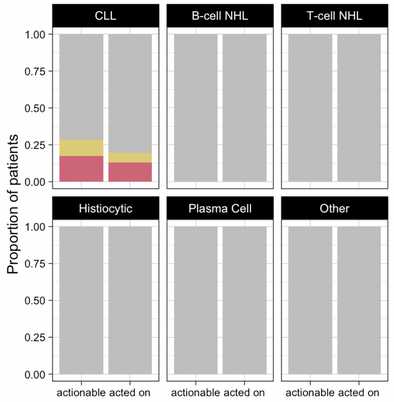
- No level A therapy sensitizing variants were identified
- 61 patients (60%) had a level B or C sensitizing variant



- 6 of 61 patients (10%) were offered biomarker-directed therapy, *e.g.*:
  - ibrutinib for DLBCL with CD78B mutation
  - romidepsin for T cell lymphoma with TET2 mutation
  - ruxolitinib for T cell lymphoma with JAK2 fusion

Therapy Resistant Variants

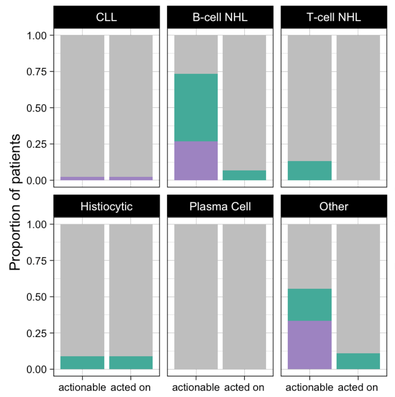
- 13 patients had a level A or D resistance variant
- All 13 patients had chronic lymphocytic leukemia (CLL)



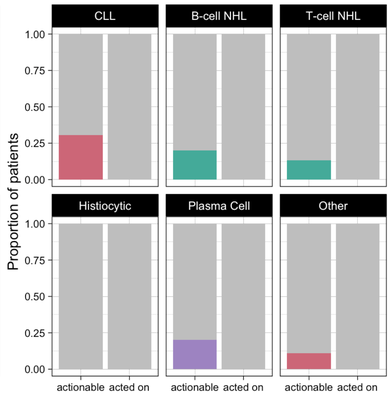
- In 9 of 13 patients (69%), presence of a resistant variant led to therapy discontinuation or influenced future therapy
- In another 4 patients, absence of a resistant variant influenced choice of therapy

Variants of Diagnostic, Prognostic, and Genetic Significance

Variants of diagnostic significance



Variants of prognostic significance



- 20 patients (20%) had a level B or C variant of diagnostic significance
- CGP was used to clarify diagnosis in 4 of these 20 patients (20%)
- 21 patients (21%) had a level A–C variant of prognostic significance
- CGP led to medical genetics referrals in 3 patients (3%) with mutations in *BRCA2*, *MSH6*, and *VHL*

Results

- 92 of 105 samples (88%) yielded at least one pathogenic or likely pathogenic variant
- 73 of 101 patients (72%) had at least one variant of clinical significance, *i.e.*, with therapy sensitizing, diagnostic, or prognostic significance (levels A–C) or associated with therapy resistance (levels A/D)

Patient Characteristics

Median age*, years (range)	60 (13–86)
Male sex, *n* (%)	59 (58%)
Race, *n* (%)	
Caucasian	69 (68%)
African American	19 (19%)
Asian	4 (4%)
American Indian or Alaskan Native	1 (1%)
Other/unknown	8 (8%)
Diagnosis, *n* (%)	
CLL	46 (46%)
B-cell NHL	15 (15%)
T-cell NHL	15 (15%)
Histiocytic neoplasms	11 (11%)
Plasma cell neoplasms	5 (5%)
Other	9 (9%)
CGP result to therapy change†, days (range)	26.5 (1–105)
CGP result 1–30 days before death, *n* (%)	11 (11%)
CGP result after death, *n* (%)	12 (12%)
Deceased‡, *n* (%)	35 (35%)

*at time of testing; ‡at time of data cut-off;
†among patients with change in therapy based on therapy sensitizing variant or resistance mutation

Conclusions

- Comprehensive genomic profiling of non-myeloid hematologic malignancies identified variants of clinical significance in 72% of patients
- CGP led to changes in practice in 22% of patients
- Therapy resistant variants were more likely to influence therapy (69%) compared to therapy sensitizing variants (10%)
- CGP was often sent late in the clinical course
- CGP can be useful for non-myeloid hematologic malignancies, but only if applied in the appropriate clinical setting