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Use of Precision Medicine Molecular Profiling of Baseline Tumor Specimen May Not Benefit Outcomes in Children With Relapsed or Refractory Pediatric Sarcomas

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Abstract

Given the poor prognosis of pediatric patients with relapsed or refractory sarcomas, discovery and implementation of innovative approaches and tools to guide therapy are urgent needs. This retrospective pilot study evaluated the impact of relapse and refractory therapies aligned with molecular characterization of biopsies collected at the time of primary diagnosis.

RESULTS

Molecular profile-based drug selection for relapse or refractory therapy using tumor collected at diagnosis may not predict overall survival

In part 1 of the analysis, two subjects received therapies aligned with the genomic diagnostic recommended therapies (score of 1). Six subjects did not receive any therapies recommended or contraindicated based on the molecular testing results or received both recommended and potentially contraindicated therapies (score of 0). One subject received a potentially contraindicated therapy (score of –1; Supplementary Table S1 online). A Cox regression analysis revealed no linear trend in overall survival (hazard ratio = 0.8; $P = 0.79$) among subjects who received therapies (1) consistent with tumor molecular testing, (2) inconsistent, or (3) potentially contraindicated therapies (Figure 1a).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

J.C. wrote the manuscript and performed the research. L.C. analyzed the data. J.Z. performed the research. M.M. designed the research. K.P. designed the research. M.M. designed the research. L.L. designed the research and analyzed the data. J.R. designed the research.

Additional Supporting Information may be found in the online version of this article.

In part 2 of the analysis, five subjects received at least one therapy aligned with the genomic diagnostic results (score of 1). Four subjects received therapies not aligned with the molecular diagnostic results (score of 0; Supplementary Table S1 online). The Cox regression analysis revealed no difference in overall survival (hazard ratio = 1.41; $P = 0.66$) between subjects who received relapse or refractory therapies consistent with tumor molecular testing and those who received therapies not aligned with molecular testing results (Figure 1b).

Molecular profile of relapsed tumor sample shows different genetic profile and drug recommendations

Although the analysis above was performed using the tumor molecular testing from specimens obtained at or near a subject's diagnosis, one subject also had tumor molecular testing performed on a specimen representing relapsed or refractory disease. This was an 11-year-old male with a pulmonary relapse of osteosarcoma who had tumor molecular profiling done on both a specimen from diagnosis as well as a specimen from relapse. Compared to the specimen collected at diagnosis, the relapse specimen shows additional cyclin E1 and MYC copy number gains, elevated mRNA expression of TOPO IIa, and a decreased expression of carbonic anhydrase IX (Figure 2). Hence, there were new drugs indicated by molecular analysis of the relapse specimen, such as doxorubicin and bevacizumab, which were not provided by analysis of the initial diagnosis specimen alone.

DISCUSSION

Although there is great optimism that the use of a precision medicine approach in pediatric patients with aggressive cancers will improve patient outcomes, there are challenges and caveats to this method. In this retrospective pilot study, we found that subjects who received therapies aligned with tumor molecular testing from specimens obtained at original diagnosis in the setting of relapsed or refractory disease did not have improved overall survival. Furthermore, the molecular diagnostic analyses of tumor specimens from diagnosis and relapse from a single subject revealed different results associated with distinct drug recommendations between the two samples. Given the shift in malignant cell biology after exposure to chemotherapy, it stands to reason that obtaining a tumor sample from relapsed or metastatic disease sites for molecular testing and ultimately guiding therapeutic decision-making is paramount.

As this was a retrospective study, therapy decisions for the eight deceased patients were not driven by the molecular diagnostic profiles; the profiles for this exploratory pilot study were obtained after their deaths. Prospective studies are ongoing to assess whether molecular testing guided therapy will further improve the efficacy of the therapy. In addition, further studies with larger sample sizes and additional outcome measures are required to fully elucidate and define the impact of using a precision medicine approach for therapeutic decision-making in pediatric patient populations.

METHODS

This study was approved by the Indiana University School of Medicine Institutional Review Board (#1501467439). A retrospective review of the medical records and molecular diagnostic analysis from nine pediatric subjects with relapsed, refractory, or rare sarcomas was completed. The molecular diagnostic analysis was performed using specimens obtained at or near a subject's diagnosis. Eight of the specimens were samples collected at diagnosis and one of the specimens was from a local control surgery 3.5 months after the subject's initial diagnosis. Eight of the nine subjects were deceased at the time of analysis.

Molecular diagnostic results were obtained using a Clinical Laboratory Improvement Amendment-approved, next-generation sequencing cancer diagnostic test. Recommended and potentially contraindicated cancer therapies provided in the test report are based upon the individual's tumor genetic variants, copy number variants, gene fusions, mRNA expression, and protein expression. These recommendations are supported by literature on known biomarker/drug associations and published therapeutic investigations. Potentially contraindicated therapies are defined as those drugs that will likely not provide clinical benefit. The therapeutic recommendations resulting from the clinical molecular diagnostic results were compared to the cancer therapies each subject received and the outcome of overall survival was ascertained.

In part 1 of the analysis, subjects were assigned a score of 1 if they received at least one molecular diagnostic recommended therapy and no potentially contraindicated therapies. A score of –1 was assigned if a subject received at least one therapy that was potentially contraindicated and no therapies aligned with the molecular testing results. A score of 0 was assigned if a subject did not receive any recommended or contraindicated therapies or received both recommended and contraindicated therapies.[1]

In part 2 of the analysis, the potentially contraindicated therapies were excluded from scoring of the subjects. A score of 1 was assigned if a subject received at least one therapy aligned with the molecular diagnostic recommended therapies. If a subject did not receive any recommended therapies, he or she received a score of 0.[1]

Two Kaplan-Meier overall survival curves for the nine subjects were plotted by the "survival" package in R software. A Cox regression analysis was used to test and estimate the hazard ratio for the linear trend of score (1, 0, –1) in the first analysis. In the part 2 analysis, the hazard ratio was tested and estimated between score 1 and 0.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

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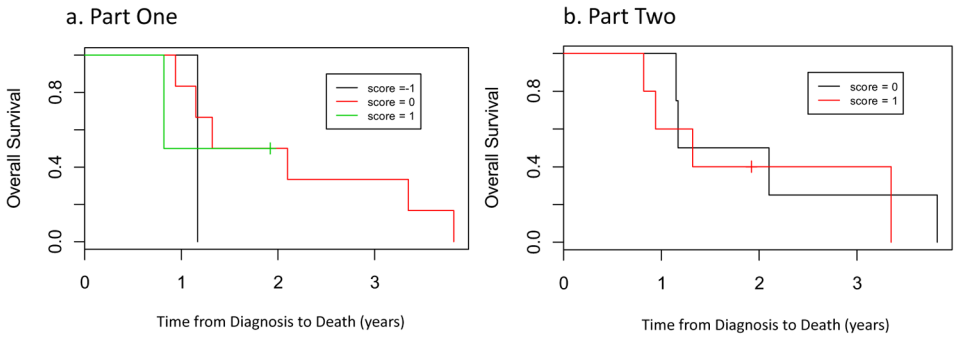
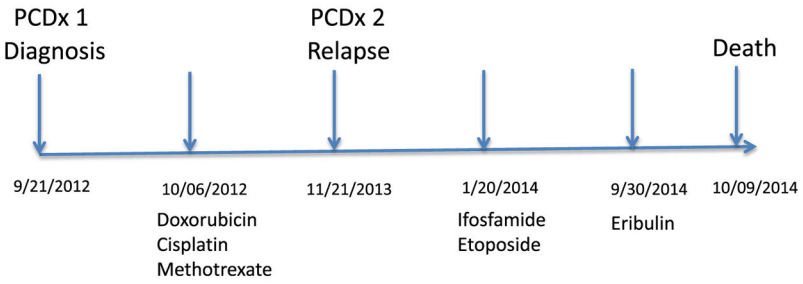


Hazard Ratios and P-values:

- Part One: HR = 0.80, p = 0.79
- Part Two: HR = 1.41, p = 0.66

Figure 1.

Kaplan-Meier curves of overall survival. (**a**) Score of 1 indicates a subject received at least one drug aligned with the molecular diagnostic testing results and no potentially contraindicated therapies. Score of −1 indicates a subject received at least one therapy that was potentially contraindicated and no therapies aligned with testing results. Score of 0 indicates a subject did not receive drugs aligned with or contraindicated by molecular diagnostic testing results or received both recommended and contraindicated therapies. (**b**) Score of 1 indicates a subject received at least one drug aligned with the molecular diagnostic testing results. Score of 0 indicates a subject did not receive any drugs aligned with the molecular diagnostic testing results.



PCDx 1 Summary (mostly failed QC)
Protein expression: hENT1 negative, TLE3 positive, TOP1 positive
Recommended therapies: docetaxel, paclitaxel, topotecan, irinotecan
Potentially contraindicated therapies: gemcitabine

PCDx 2 Summary
Copy number variation: cyclin E1 gain, MYC gain
High mRNA expression: TUBB3, survivin, TOPOIIa, TS
Protein expression: hENT1 negative, CA IX negative, TOP1 positive
Recommended therapies: epirubicin, doxorubicin, bevacizumab, topotecan, irinotecan
Potentially contraindicated therapies: gemcitabine, cisplatin, carboplatin, vinorelbine, capecitabine, pemetrexed

Figure 2.
A subject with tumor molecular profiling at diagnosis and relapse.