Biomarkers and targetable mutations

PROGRESS TOWARD PERSONALIZED ONCOGENOMICS

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TRIAL SUMMARY: Biomarkers to predict response to docetaxel

Khalaf DJ, Herberts C, Vandekerkhove G, et al. Determining biomarkers of response to docetaxel for patients with metastatic castration-resistant prostate cancer using circulating cell-free tumor DNA. Canadian Association of Medical Oncology Annual Meeting. April 26, 2018, Toronto. Abstract 42.

This study aimed to assess whether somatic and germline genomic alterations, identified using plasma circulating cell-free tumour DNA (ctDNA), are predictive for response to docetaxel in metastatic castration-resistant prostate cancer (mCRPC). The study enrolled patients commencing docetaxel for mCRPC between November 2015 and August 2017. A plasma sample for ctDNA analysis was collected before initiation of docetaxel. Targeted sequencing of 73 prostate cancer-relevant genes was performed on leukocyte DNA (germline) and plasma cell-free DNA. Patient records were reviewed for baseline clinical characteristics, prostate-specific antigen (PSA) response (≥50% decline from baseline), and time to PSA progression (TTPP) using Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.

All of the 33 patients enrolled had received prior abiraterone or enzalutamide and none had received prior taxanes. Median age was 70 years, 30% had Eastern Collaborative Oncology Group (ECOG) performance status of 2; 67% had bone metastasis and 9% had liver metastasis.

Results: Samples analyzed from the 33 patients identified deleterious genomic alterations, including: BRCA2 or ATM defects in 12% of patients, TP53 alterations in 39%, RB1 loss in 21%, PTEN loss in 21%, and androgen receptor (AR) amplification in 42%. Following initiation of docetaxel, the PSA response rate (RR) was 39%, median TTPP was 4.3 months and median overall survival (OS) was 10.6 months. High ctDNA fraction (>20%), AR amplification and TP53 alterations were associated with a trend toward worse OS, but were not associated with RR or TTPP <3 months (see **Table 1**). PTEN deletion was associated with a trend toward worse RR. BRCA2/ATM defects were associated with a trend toward improved TTPP <3 months.

The analysis suggested associations between outcomes

with docetaxel therapy and genomic alterations in BRCA2/ATM, TP53, RB1, PTEN and AR. Accrual is ongoing in order to further evaluate these associations and identify potential genomic predictors of response and resistance.

TABLE 1: Genetic alternations and time to PSA progression

Alteration	RR (%)	P	TTPP <3 months (%)	P	HR for OS (95% CI)	P
BRCA2/ATM	50	0.643	0	0.129	0.74 (0.17–3.21)	0.686
TP53	46.2	0.522	30.1	0.794	2.19 (0.96–5.03)	0.064
RB1	42.9	0.833	14.3	0.222	1.46 (0.59–3.61)	0.410
PTEN	16.7	0.126	42.9	0.542	1.71 (0.66–4.44)	0.267
AR	28.6	0.168	42.9	0.301	2.15 (0.94–4.92)	0.070
ctDNA fraction >20%	33.3	0.663	33.3	1.000	1.99 (0.85–4.65)	0.112

ctDNA=circulating tumour DNA; AR=androgen receptor; RR=response rate; HR=hazard ratio.

TRIAL SUMMARY: Personalized oncogenomics in breast cancer

LeVasseur N, Shen Y, Zhao EY, et al. Whole genome sequencing in metastatic breast cancer – lessons learned from the BC cancer personalized oncogenomics program. Canadian Association of Medical Oncology Annual Meeting. April 26, 2018, Toronto. Abstract 44.

In breast cancer, there is increasing interest in genomic profiling to identify therapeutically targetable alterations. In this and other areas of personalized medicine, the clinical relevance of whole-genome sequencing (WGS) and RNA sequencing, as compared to targeted next generation sequencing (NGS), remains uncertain. Moreover, refined data is needed to identify which patients benefit most from molecular profiling.

Informative and actionable findings from WGS in metastatic breast cancer patients between 2012 and 2017 were reviewed and compared to pre-existing FoundationOne and MSK-IMPACT (Memorial Sloan Kettering—Integrated Mutation Profiling of Actionable Cancer Targets) targeted panels. The data around these findings was compiled using an RNA/DNA heat map. Single nucleotide variants (SNV) mutation signature and mutational burden were compared across histologic and molecular subtypes, and between age-driven and non-age driven tumours.

Results: WGS of 139 patients with metastatic breast cancer revealed that 77% of actionable items arose from expression data, 60% from mutations, 45% from copy number changes, 28% from mutation signature, mutation burden, or homologous recombination deficiency (HRD), and 5% from structural variants (SV). The majority (7,616/7,998 or 95%) of mutations were only detected by WGS, and most of these were passenger mutations. Driver mutations identified in WGS were also identified in the FoundationOne (339/7,998 or 4%) and MSK-IMPACT panels (201/7,998 or 3%). No significant differences in mutation burden were identified among subtypes, although tumours whose somatic mutagenesis was driven predominantly by age-related processes displayed lower mutation burdens. Elevations of HRD-associated mutation signatures of SNV/SV were identified more frequently in triple-negative and basal-like tumours.

Most actionable mutations were identified with pre-existing targeted panels. Expression data represents a significant proportion of actionable information obtained from WGS. Mutational burden did not vary significantly among subtypes. Signature properties and their relation to molecular subtypes remains an interesting arena for clinical application.

COMMENTARY: Understanding tumour biology is the cornerstone of modern personalized oncology. Despite advances in identifying genetic aberrations in metastatic breast and prostate cancer, the clinical value for determining appropriate management of individual patients is not well established. Differentiating predictive from prognostic biomarkers remains an active area of investigation. Similarly, for many cancer sites, there are not yet clear answers about what makes an aberration a driver mutation versus a passenger mutation.

In their study, Khalaf et al describe attempts to find a predictive biomarker for response to docetaxel, a chemotherapy regimen now commonly used in metastatic prostate cancer. The topic is of utmost relevance, given the heterogeneity of prostate cancers. With circulating tumour DNA (ctDNA), a novel, noninvasive, and exciting approach to obtaining genetic information about the tumour, we are now able to isolate certain genetic mutations, such as TP53, BRCA, and androgen receptor amplification. These mutations have been associated with worse progression-free survival (PFS) and resistance to hormone treatments, such as abiraterone and enzalutamide.

Although the preliminary data Dr. Khalaf presented at the CAMO conference does not identify a clear predictive biomarker, he was able to show that a higher burden of ctDNA may be prognostic, as it is associated with poorer survival. In addition, while the presence of TP53 is associated with resistance to hormone therapy, this was not the

case with docetaxel, further highlighting the complexity and heterogeneity of precision medicine.

Dr Levasseur et al's study on whole genome sequencing in metastatic breast cancer presents lessons learned from the BC Cancer Personalized Oncogenomics (POG) program. Here too, the benefits and challenges of personalized medicine are evident. The POG program in BC is a pilot research project, collecting genetic information from tumours of patients with advanced cancer to analyze the molecular abnormalities that drive carcinogenesis and identify potentially actionable mutations. More often than not, analysis provides additional information to help understand the biology of cancer, but seldom do findings translate into additional therapeutic benefit in clinical practice.

In this study, whole-genome sequencing of 139 patients with metastatic breast cancer revealed 77% actionable items, many of which are RNA expression changes that do not appear on standard target panels. Only very rarely does the information found via POG analysis enable targeted drug therapy. This raises the issue of what constitutes a driver mutation vs a passenger mutation, and our current understanding of tumour biology does not yet enable us to differentiate them, even with modern technology. The large randomized phase 2 SHIVA trial[1] reflects many of these conclusions and reminds us that, while personalized oncology is emerging as a new standard of care in many cancer sites, it is imperative to recognize that one size does not fit all. Much more research is needed in this area.

References

1. Le Tourneau C, Delord JP, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol* 2015 Oct;16(13):1324–34.

IN BRIEF

Already known

- There is increasing interest in genomic profiling to identify targetable alterations in prostate and breast cancer.

What these studies showed

- In prostate cancer, no predictive biomarker was found as a reliable predictor of response to docetaxel, though other markers may have prognostic value.
- In breast cancer, whole-genome sequencing helped to better understand cancer biology, but rarely produced findings that could translate into clinical benefit.

Next steps

- Much more research is needed to bring personalized oncology into being.