LUNG CANCER

SLFN11: a new synthetic lethal target?

The standard of care for patients with small-cell lung cancer (SCLC) has remained unchanged for several decades. Now, the findings of a phase II study reveal the potential of biomarker-guided use of temozolomide (TMZ) in combination with veliparib in patients with tumours expressing schlafen family member 11 (SLFN11), which promotes cell death following DNA damage.

In this trial, 104 unselected patients with relapsed and/or refractory SCLC were randomized to receive either TMZ plus placebo or TMZ plus the poly(ADP-ribose) polymerase (PARP) inhibitor veliparib. Patients in the TMZ plus veliparib group had no significant improvement in overall survival (8.2 months versus 7.0 months in the TMZ plus placebo group; $P = 0.5$). In a prespecified subgroup analysis, however, patients in the TMZ plus veliparib arm with SLFN11-positive tumours, as defined using immunohistochemistry ($n = 12$), had improved progression-free survival (5.7 months versus 3.6 months; $P = 0.009$) and overall survival (12.2 months versus 7.5 months; $P = 0.014$) relative to patients with SLFN11-negative tumours. PARP1 expression was detected in the majority of samples analysed (87%) and was not correlated with patient outcomes.

The addition of veliparib to TMZ resulted in an increased risk of several grade 3–4 haematological toxicities, including thrombocytopenia, neutropenia, and leukopenia. No notable differences in risk of grade 3–4 non-haematological toxicities were observed.

These findings, albeit only from a small subgroup of patients, provide prospective evidence that SLFN11 expression is a biomarker of responsiveness to PARP inhibition in patients with SCLC. The authors note that adjustments in the dose and/or type of PARP inhibitor used might confer further improvements in the outcomes of patients with SLFN11-positive SCLC.

Peter Sidaway

ORIGINAL ARTICLE Pietanza, C. M. et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2018.77.7672 (2018)

PAEDIATRIC CANCER

Sodium thiosulfate halves the risk of cisplatin-induced hearing loss

Cisplatin is an effective treatment of childhood hepatoblastoma, but can cause severe and permanent ototoxicity; in paediatric patients, even minor hearing loss can drastically affect learning, development, and quality of life (QOL). Now, results of the randomized, phase III SIOPEL 6 trial demonstrate that sodium thiosulfate (STS) has considerable efficacy in preventing cisplatin-induced hearing loss.

In SIOPEL 6, 109 children with standard-risk hepatoblastoma received 4 preoperative and 2 postoperative cycles of cisplatin (80 g/m^2), with 57 patients also receiving STS at 20 g/m^2 intravenously 6 h after cisplatin administration. Delayed administration of STS was chosen on the basis of preclinical and clinical evidence in order to maximize the otoprotective effect while minimizing potential tumour-protective effects.

"The most significant finding of this study is that it confirms that delayed treatment with STS protects the majority of children from lifelong cisplatin-induced hearing loss," states lead author Penelope Brock. Hearing loss of any grade (according to the Brock 4-point scale) occurred in 33% of patients who received STS versus 63% of those treated with cisplatin alone — a relative risk reduction of 48% ($P = 0.002$). Moreover, 3-year event-free survival (82% versus 79%) and overall survival (98% versus 92%) were similar in the STS and cisplatin-only groups.

"This study should dispel the fears of delayed STS tumour protection, raised by a post-hoc analysis of the ACCL0431 trial," says Brock. "Notably, this drug could most profoundly improve the QOL of patients in the developing world, where cisplatin is extensively used but the devastating personal, educational, and social consequences of hearing loss often remain unaddressed," she adds, concluding, "ultimately, STS could be made available to all adults and children receiving cisplatin chemotherapy."

David Killock

ORIGINAL ARTICLE Brock, P. R. et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. *N. Engl. J. Med.* **378**, 2376–2385 (2018)

PROSTATE CANCER

AR-V7 detection guides treatment

Alternative splicing of the gene encoding the androgen receptor (AR) has been proposed as a mechanism of therapeutic resistance to AR signalling (ARS) inhibitors. The splice variant AR-V7 lacks the ligand-binding domain, leading to constitutive activation of ARS. Howard Scher and colleagues have now validated nuclear AR-V7 in circulating tumour cells (CTCs) as a marker to guide treatment decisions for patients with metastatic castration-resistant prostate cancer (mCRPC).

Blood samples were obtained from patients with mCRPC before starting treatment with ARS inhibitors ($n = 70$) or with a taxane ($n = 72$). Patients in which ≥1 CTC with an intact nucleus and nuclear staining for AR-V7 was detected in ~1 ml of blood were defined as AR-V7$^+$. Overall survival data were analysed separately for patients with high-risk disease ($n = 70$) or low-risk disease ($n = 72$). Patients with AR-V7$^-$ high-risk disease had a longer median overall survival with ARS inhibitors than with taxanes (16.9 months versus 9.7 months; HR 2.38; $P = 0.02$), whereas patients with AR-V7$^+$ high-risk disease had a longer median overall survival with taxanes than with ARS inhibitors (14.3 months versus 5.6 months; HR 0.35; $P = 0.03$). In the low-risk group, the number of AR-V7$^+$ patients was not sufficient to estimate differences in survival between treatments according to the presence of AR-V7. Patients with low-risk disease should receive taxanes if they are AR-V7$^+$ or ARS inhibitors if they are AR-V7$^-$.

The CTC detection test used in this study is commercially available; Scher hopes that it is implemented in routine clinical practice. "Our focus was to show that the use of the biomarker test result to inform the choice of treatment could lead to an improved outcome for patients relative to not using the test result," Scher comments, adding "AR-V7 status alone does not explain all of the mechanisms of resistance to AR inhibitors. Going forward, we will take the approach used in this study to identify and validate other markers of resistance, including tumour heterogeneity and genomic instability."

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ORIGINAL ARTICLE Scher, H. I. et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2018.1621 (2018)