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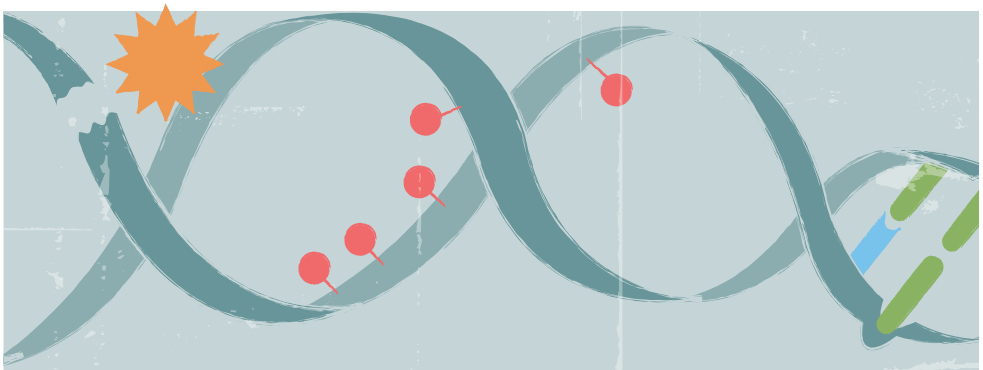

BLADDER CANCER

Mutations in DNA-damage-repair pathways confer platinum sensitivity

> “....the presence of DDR mutations is associated with better outcomes with platinum-based chemotherapy”

Platinum-based chemotherapy remains the standard-of-care treatment approach for patients with advanced-stage urothelial carcinoma; however, despite the substantial risk of adverse events and the fact that many patients fail to respond to such treatments, no reliable biomarkers of a response to therapy have been developed. Now, researchers have demonstrated that the presence of somatic mutations in genes that encode DNA damage response or repair (DDR) proteins, the majority of which confer a reduction in the ability to repair DNA damage, is associated with a significant improvement in both progression-free survival (PFS), and overall survival.

Researchers performed next-generation sequencing (NGS) using the MSK–IMPACT platform to investigate the prevalence of somatic DDR alterations in pretreatment tumour tissue samples. Lead author Jonathan Rosenberg explains the rationale for this approach: “We have previously shown that patients with bladder cancer receiving neoadjuvant cisplatin-based chemotherapy who have mutations in DNA repair genes have outstanding pathological responses, such as major downstaging, disappearance of invasive cancer, or eradication.” Furthermore: “We sought to determine whether these findings are applicable to patients with metastatic disease treated with platinum-based chemotherapy.”

NGS data were then analysed for the presence of mutations in 34 DDR-associated genes, including, among others, those involved in nucleotide-excision repair, mismatch repair, or homologous recombination. A total of 47 of the 100 patients included in this study had one or more DDR alteration, of which ten had two, and nine had at least three mutations. Patients with at least one DDR alteration had significantly longer PFS (9.3 versus 6.0 months; $P = 0.007$) and overall survival (23.7 versus 13.0 months; $P = 0.006$) with platinum-containing therapy compared with patients with no detectable DDR alterations. Furthermore, patients with DDR alterations were more likely to have nodal metastases, and less likely to have visceral metastases than those without DDR alterations. Rosenberg summarizes, “The results indicate that the presence of DDR mutations is associated with better outcomes with platinum-based chemotherapy.”

A further analysis of the mutational burden of patient subgroups revealed that patients with DDR mutations had a significantly higher number of mutations and copy number alterations in the 341 genes analysed using NGS. This finding suggests that the presence of somatic DDR alterations might also confer a more-favourable response to immunotherapy, although this has yet to be investigated.

In conclusion, these findings demonstrate that the presence of somatic DDR mutations confers an improved response to platinum-containing therapies in patients with advanced-stage disease, reflecting similar observations in patients with organ-confined disease. When asked about future directions of this work, Rosenberg explains: “We plan to externally validate these findings in a randomized phase III study of gemcitabine or cisplatin with or without bevacizumab: this study has completed accrual and data are maturing. If validated, this research may provide a way to identify patients who are predicted to derive maximum benefit from platinum-based chemotherapy and enable patients without these mutations to receive treatment using alternative approaches.”

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ORIGINAL ARTICLE Teo, M. Y. *et al.* DNA damage response and repair gene alterations are associated with improved survival in patients with platinum-treated advanced urothelial carcinoma. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-16-2520 (2017)