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Uncovering the role of mismatch repair deficiency and microsatellite instability in urothelial carcinoma

Filippo Ghelardi, Patrizia Giannatempo, Filippo Pietrantonio

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Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Correspondence to
Dr Filippo Pietrantonio; filippo.pietrantonio@istitutotumori.mi.it

Deficient mismatch repair (dMMR) and microsatellite instability-high (MSI-H) status are among the strongest predictive factors for immune checkpoint inhibitors (ICIs) benefit in patients with advanced solid tumours, leading to recent agnostic Food and Drug Administration approval of pembrolizumab in patients with previously treated dMMR/MSI-H disease. Although upfront and/or reflex MSI testing is recommended in patients with gastrointestinal cancers, data supporting the clinical usefulness of universal MSI testing for upfront immunotherapy in patients with advanced solid tumours are lacking, partly due to the rarity of the molecular subgroup in several tumour types. Nonetheless, drawing from experience in the management of patients with gastrointestinal cancers, early identification of this subset of patients with exquisite ICIs sensitivity deeply influenced the therapeutic management and improved life expectancy, with a significant reduction in toxicity burden as compared with chemotherapy.[1] Moreover, the prognostic role of MSI status is established in patients with gastric and colorectal cancers, with a positive association between dMMR/MSI-H status and survival following curative resection.[2 3] In line with this, for most patients with radically resected average-risk stage II colorectal cancer and dMMR/MSI-H status, adjuvant chemotherapy is not recommended by major global guidelines.[4]

Scarce data are available on dMMR/MSI-H status in urothelial carcinoma (UC), mostly deriving from small, retrospective series. Urakami and colleagues retrospectively assessed MMR status on 143 surgical specimens of patients with upper urinary tract urothelial carcinoma (UTUC) who underwent curative surgery at a Japanese oncological centre highlighting MMR protein loss, mostly Lynch syndrome-related MSH2/MSH6 loss, in 5% of cases.[5]

Here, Chandran and colleagues highlighted a consistently higher rate of dMMR in UTUC (9%) compared with bladder cancer (BC; 2.3%).[6] Similar discrepancies between UTUC and BC were obtained by analysing MSI status with PCR; specifically, MSI-H status was identified in 3.04% and 0.86% of localised and metastatic BC, respectively, with higher rate in UTUC, both for localised (15.6%) and metastatic disease (4.35%). The difference in dMMR/MSI-H rates in localised versus advanced disease mirrors the literature in gastrointestinal tumours and may be explained by better outcomes of MSI-H UC patients following radical surgery, as outlined in most of the included studies. Consistently, patients with dMMR/MSI-H disease may benefit from treatment de-intensification or the use of ICIs as early as possible. The Authors recall recent advances in the management of early dMMR/MSI-H colorectal and gastric cancers, where the concept of immune-ablation and non-operative management is being investigated with extremely promising results, sparing patients from life-altering surgical procedures.[7]

In the metastatic setting, 17 studies evaluated ICIs with promising results in patients with dMMR/MSI-H disease, with a response rate of 64.7% and most responses being durable. On the contrary, chemotherapy was associated with significant rates of resistance, thus reinforcing the hypothesis that the anticipation of ICI to early lines of treatment may be beneficial in terms of survival outcomes and may help spare patients from unnecessary toxicities.

Upfront pembrolizumab plus the antibody-drug conjugate enfortumab-vedotin demonstrated improved efficacy versus standard chemotherapy in a recently reported pivotal trial for patients with previously untreated metastatic urothelial carcinoma (mUC).[8] In this trial, the survival benefit appeared

maintained irrespective of programmed death-ligand 1 combined positive score (CPS) status, paving the way for the approval of such combination as upfront therapy in all patients with mUC. While this may allow patients with MSI-H disease to receive upfront ICIs in the clinical practice, it is worth highlighting that patients with dMMR/MSI-H UC may deserve dedicated clinical trials and therapeutic strategies in the future. Moving forward, as immunotherapy becomes increasingly available for all patients in the first-line setting, it becomes even more imperative to establish recommendations for genetic testing, particularly for patients with a family history of Lynch syndrome-related tumours, a familiarity with UC, and UTUC. Furthermore, drawing from recent experience in early-stage dMMR/MSI-H gastrointestinal tumours, upfront identification of this subset of patients with immune-sensitive tumours may lead to dedicated clinical trials with neoadjuvant ICI-based approaches, potentially paving the way for the adoption of non-operative strategies.

In conclusion, MMR/MSI testing in routine clinical practice may lead to personalise the management of patients with UC and improve their outcomes.

X Filippo Ghelardi @FilippoGhelard and Filippo Pietrantonio @FilippoPietran4

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ORCID iD

Filippo Pietrantonio http://orcid.org/0000-0002-8530-8420

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