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Original Research

Clinical and molecular characterisation of hereditary and sporadic metastatic colorectal cancers harbouring microsatellite instability/DNA mismatch repair deficiency

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Abstract ***Background:*** Patients treated with chemotherapy for microsatellite unstable (MSI) and/or mismatch repair deficient (dMMR) cancer metastatic colorectal cancer (mCRC) exhibit poor prognosis. We aimed to evaluate the relevance of distinguishing sporadic from Lynch syndrome (LS)-like mCRCs.
Patients and methods: MSI/dMMR mCRC patients were retrospectively identified in six French hospitals. Tumour samples were screened for MSI, dMMR, *RAS*/*RAF* mutations and *MLH1* methylation. Sporadic cases were molecularly defined as those displaying MLH1/PMS2 loss of expression with *BRAF*V600E and/or *MLH1* hypermethylation and no MMR germline mutation.
Results: Among 129 MSI/dMMR mCRC patients, 81 (63%) were LS-like and 48 (31%) had sporadic tumours; 22% of MLH1/PMS2-negative mCRCs would have been misclassified using an algorithm based on local medical records (age, Amsterdam II criteria, *BRAF* and MMR statuses when locally tested), compared to a systematical assessment of MMR, *BRAF* and *MLH1* methylation statuses. In univariate analysis, parameters associated with better overall survival were age ($P < 0.0001$), metastatic resection ($P = 0.001$) and LS-like mCRC ($P = 0.01$), but not *BRAF*V600E. In multivariate analysis, age (hazard ratio (HR) = 3.19, $P = 0.01$) and metastatic resection (HR = 4.2, $P = 0.001$) were associated with overall survival, but not LS. LS-like patients were associated with more frequent liver involvement, metastatic resection and better disease-free survival after metastasectomy (HR = 0.28, $P = 0.01$). Median progression-free survival of first-line chemotherapy was similar between the two groups (4.2 and 4.2 months; $P = 0.44$).
Conclusions: LS-like and sporadic MSI/dMMR mCRCs display distinct natural histories. MMR, *BRAF* mutation and *MLH1* methylation testing should be mandatory to differentiate LS-like and sporadic MSI/dMMR mCRC, to determine in particular whether immune checkpoint inhibitors efficacy differs in these two populations.

1. Introduction

Microsatellite instability (MSI) is caused by the deficiency of the mismatch repair (MMR) system, resulting from a germline mutation in MMR genes (*MLH1*, *PMS2*, *MSH2*, *MSH6*) predisposing to Lynch syndrome (LS), or an epigenetic inactivation of *MLH1*. Sporadic MSI/MMR-deficient (dMMR) colorectal cancer (CRC), unlike LS-related CRC, is associated with the *BRAF*V600E mutation, through its association with CIMP (CpG island methylator phenotype) [1]. MMR genes germline mutation cannot always be detected in LS and the definition of sporadic MSI/dMMR CRCs and CRCs presumed to be LS-related (i.e. Lynch-like) has evolved over time, from clinical criteria to a tailored approach with *BRAF* and *MLH1* methylation testing for CRCs showing a loss of MLH1 expression [2–5].

Stage II MSI/dMMR CRC has a favourable prognosis. 5-Fluorouracil-based adjuvant chemotherapy (5-fluorouracil alone, with leucovorin or levamisole) is ineffective on stage II MSI/dMMR CRCs [6]. However, the addition of oxaliplatin to fluoropyrimidines seems associated with a survival benefit for patients with high-risk stage II or stage III MSI/dMMR CRCs [7,8]. Sensitivity to fluoropyrimidine may differ between sporadic and hereditary stage III MSI/dMMR CRCs [8,9]. In metastatic setting, the poor prevalence of MSI/dMMR (3–5%) hampers the evaluation of its prognostic value, and results from early studies were inconsistent [10–14]. The pooled analysis of four phase III studies in first-line treatment of mCRC demonstrated that dMMR is associated with reduced progression-free survival (PFS) and overall survival (OS), with an insignificant negative effect of *BRAF*V600E among MSI mCRCs [15]. Thus, the impact of *BRAF*V600E on MSI CRCs remains controversial.

While immune checkpoint inhibitors (ICKs) have demonstrated promising efficacy for MSI tumours, unresolved issues persist concerning molecular and clinical heterogeneity among MSI/dMMR mCRC patients [16,17]. In our multicentre retrospective study, we aimed to evaluate a molecular definition of sporadic and inherited MMR deficiency of MSI/dMMR mCRC patients, with a particular interest in its clinical relevance before the era of immunotherapy.

2. Material and methods

2.1. Study population

This retrospective study was conducted in six French hospitals. All patients with locally determined MSI and/or dMMR mCRC were eligible. Tumour specimen