POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JULY 01 2018

Abstract 2743: Accumulation of predicted neoantigens by MMR deficiency triggered by temozolomide treatment of human colorectal cancer

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Cancer Res (2018) 78 (13_Supplement): 2743.

https://doi.org/10.1158/1538-7445.AM2018-2743

Abstract

Recent clinical trials have reported that alkylating agents, such as dacarbazine and temozolomide (TMZ) are effective in 10-15% metastatic colorectal cancer (mCRC) patients. In a retrospective analysis of 105 mCRC patients enrolled in clinical trials with alkylating agents, we saw that O6-methylguanine-DNA- methyltransferase (MGMT, the enzyme responsible for repairing drug induced DNA adducts), promoter methylation and protein status could identify a patient subgroup more likely to benefit from these drugs. However, the time to progression of patients treated with alkylating agents was limited by the onset of resistance. In order to identify determinants of response to these agents, we tested TMZ in a collection of 47 molecularly annotated CRC cell lines. We found that only cells displaying mismatch repair (MMR) proficiency as well as promoter methylation and transcriptional silencing of MGMT were sensitive to the treatment. Sensitive cells were chronically exposed to TMZ until the emergence of resistance occurred in seven out of ten models. We identified the mechanisms of acquired drug resistance to be either re-expression of MGMT and/or mutations in MMR genes. Biopsies of eight patients, relapsing upon TMZ based regimen after a long lasting clinical benefit (>3 months), were analyzed for MGMT re-expression and for exome or target panel next generation sequencing. These analyses confirmed the results found in preclinical models: five biopsies showed MGMT re-expression, two demonstrated mutations in the MMR genes (i.e. MSH6 or MSH2), and one displayed a mutation in BRCA2. Interestingly, biopsies and cell lines in which resistance was associated to alterations in DNA repair genes displayed increased mutational loads compared to pre-treatment samples. Despite the absence of the microsatellite switch commonly found in MMR deficient driven cancer, follow up over time in absence of drug of a subset of resistant cell line models demonstrated that those which displayed a mutation in the MMR had an accumulation of predicted neo-antigens, suggesting an increased immunogenicity. This work has implications for the design of future trials incorporating TMZ as part of a multi-modality strategy for treating MGMT deficient and MMR proficient CRC.

Citation Format: Ludovic Barault, Giovanni Germano, Simona Lamba, Giuseppe Rospo, Alessandro Magri, Federica Maione, Mariangela Russo, Giovanni Crisafulli, Chiara Falcomatà, Carlotta Cancelliere, Alice Bartolini, Giulia Lerda, Giulia Siravegna, Benedetta Mussolin, Roberta Frapolli, Monica Montone, Giovanni Randon, Filippo de Braud, Nabil Amirouchene-Angelozzi, Silvia Marsoni, Maurizio D'Incalci, Armando Orlandi, Enrico Giraudo, Andrea Sartore-Bianchi, Salvatore Siena, Filippo Pietrantonio, Alberto Bardelli, Federica Di Nicolantonio. Accumulation of predicted neoantigens by MMR deficiency triggered by temozolomide treatment of human colorectal cancer [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14-18; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2018;78(13 Suppl):Abstract nr 2743.