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Revealing potential immune responses (IRs) in patients with advanced colorectal cancer (aCRC) on first line chemotherapy: a prospective study of neutrophil to lymphocyte ratio, immune function and outcome.

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Background
Neutrophil to lymphocyte ratio (NLR), a broad measure of inflammation and immune function, predicts outcome including overall survival (OS) in aCRC but the underlying mechanisms are unclear. Better understanding of IR in these patients may identify potential responders to novel immunotherapy. We investigated whether immune function correlated to NLR and how this altered during chemotherapy.

Methods
Peripheral blood was taken from 29 aCRC patients receiving 1st line chemotherapy (baseline and 6 weeks). NLR of ≥5 was defined as high. Immune function of peripheral blood mononuclear cells (PBMCs) was determined by NK cell activity (degranulation by CD107 expression and cytotoxic potential by ^{51}Chromium release) against target tumour cells, T cell activity by IFN-γ ELISpot, cytokine secretion (Luminex) and immune cell activation (flow cytometry).

Results
High baseline NLR was associated with shorter OS compared to low NLR (6.6 vs. 18.8 months; HR=3.6 [1.25 to 10.35] p=0.0024). High NLR also correlated with a depressed IR, including decreased cytolytic activity of PBMCs (p=0.046), NK cell degranulation at baseline and decreased levels of certain immune stimulatory cytokines.

Low baseline NLR correlated with increased T cell activity against tumour-associated carcinoembryonic antigen (CEA) after 6 weeks of chemotherapy. Higher cytotoxic activity of PBMCs against target tumour cells at baseline (seen in the majority of patients with NLR <5) was associated with increased OS (p=0.04).

A drop in NLR during chemotherapy was associated with increased innate immune function as determined by NK cell degranulation (p=0.004).

Irrespective of NLR, frequency of Tregs reduced during chemotherapy and there was an increase in PD-1 expression on CD8+ T cells (p=0.043), NK cells (p=0.035) and monocytes (p=0.016).

Conclusion
This study supports the poor prognosis of a high baseline NLR in aCRC and demonstrates its association with an attenuated IR. Chemotherapy can partially reverse this phenomenon, potentially enhancing anti-tumour immunity. If chemotherapy leads to a more effective anti-tumour IR, sequential immunotherapy could exploit this.