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Review

Immunotherapy in gastrointestinal cancer: Recent results, current studies and future perspectives

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Abstract The new therapeutic approach of using immune checkpoint inhibitors as anticancer agents is a landmark innovation. Early studies suggest that immune checkpoint inhibition might also be effective in patients with gastrointestinal cancer. To improve the efficacy of immunotherapy, different strategies are currently under evaluation. This review summarises

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Checkpoint inhibitors

the discussion during the European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cancer Translational Research Meeting in Mainz in November 2014 and provides an update on the most recent results of immune therapy in gastrointestinal cancers. Knowledge of potential relationships between tumour cells and their microenvironment including the immune system will be essential in gastrointestinal malignancies. In this context, the density of T cell infiltration within colorectal cancer metastases has been associated with response to chemotherapy, and a high expression of programmed cell death ligand 1 (PD-L1) in advanced gastric cancer has been related with poor prognosis. Effective targets might include neo-antigens encoded from genes carrying tumour-specific somatic mutations. Tailored immunotherapy based on such mutations could enable the effective targeting of an individual patient's tumour with vaccines produced on demand. Other strategies considering checkpoint inhibitors have shown efficacy by targeting cytotoxic T-lymphocyte-associated protein 4 and PD-1 or PD-L1. DNA mismatch repair-deficient tumours appear to be potentially the best candidates for these therapies. Finally, the combination of oncolytic viruses with immunotherapy might boost antitumour activity as well. Further evaluation of these promising immunological therapeutic approaches will require large prospective clinical studies.

1. Introduction

The use of immune checkpoint inhibitors in the treatment of patients with malignant melanoma and non-small cell lung cancer (NSCLC) represents a landmark therapeutic innovation which led to a recent renaissance of immune-mediated anticancer strategies. Initial results suggest that this approach may also be effective in the treatment of gastrointestinal carcinomas [1–6].

In the beginning of the 1990s, the first human tumour-associated antigens (TAAs) were discovered in melanoma [7], enabling the evaluation of autologous, tumour cell-specific cytotoxic $CD8^+$ T-lymphocytes as a therapeutic approach [8]. However, in many patients the activation of the immune system via TAAs is insufficient to induce strong and durable antitumour immune responses. This is due to immune escape mechanisms, such as loss of antigen expression by the tumour cells, upregulation of regulatory T cells (Tregs), or the establishment of a tumour-induced protective microenvironment [9,10]. In contrast, enhanced maturation and activation of antigen-presenting cells (APCs, e.g. dendritic cells [DCs]) can result in an enhanced immune response [11,12]. The characterisation of tumour antigens from an individual patient has the potential of an adaptive personalised immunotherapy, based on the production and amplification of naturally or genetically modified tumour-specific T cells [13–15]. The efficacy of such immunotherapy approach has been correlated with the patient's existing individual T cell repertoire [16].

To improve immunotherapy in oncology, many different strategies are currently being evaluated. Active cellular immunotherapy includes tearing down of immunological barriers. Furthermore, the combination of chemotherapy or radiotherapy with immunotherapy may enhance the immune response [17]. This review summarises most of the oral presentations and discussions which took place at the European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Group Translational Research Meeting in Mainz, November 2014 and provides in addition an update on the most recent results of immune therapy in gastrointestinal cancers (Supplementary Table 1, Search strategy).

2. Immune cell infiltration and new molecular targets

The qualitative and quantitative analyses of tumour immune cell infiltration stimulated the research into targeted agents as well as clinical and molecular biomarkers in gastrointestinal cancers. Tumours consist of tumour cells and intratumoural stroma (ITS) [18]. Wu et al. [19] showed that a stromal gene expression signature as well as the ITS proportion quantified by morphometry in tissue sections of patient samples were correlated and could both serve as potential prognostic markers. Gastric cancer (GC) patients with high ITS were found to have poorer cancer-specific survival compared to patients with low ITS proportion. Measuring the relative amount of ITS may enable the identification of subgroups of GC patients that might respond to tumour stroma-directed therapies. Recently, tumour-infiltrating immune cells (TILs) were assessed in Epstein–Barr virus (EBV)-associated GC and an association between a high percentage of TILs and longer disease-free survival was demonstrated [20].

Recently, Halama et al. [22] investigated the phenotype of the infiltrating immune cell in the primary tumour in comparison to that found in metastases. They demonstrated that type, density and location of immune cells within primary colorectal cancer (CRC) predict survival [21]. The same group developed a score to investigate the prognostic and predictive significance of TIL densities at the invasive edge of CRC liver