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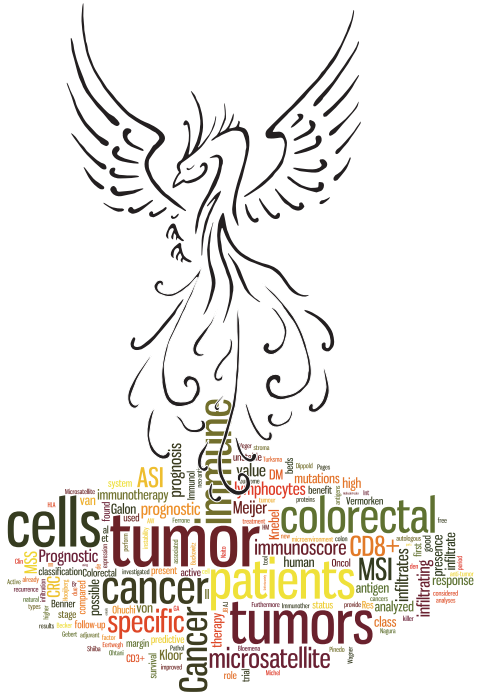
Discussion part 3
ASI trial for colorectal cancer patients



Vermorken et al. published the results of a large multicentre trial testing ASI treatment in Colorectal (CRC) patients in 1999. A median follow-up of 5.3 years showed a significant benefit of ASI compared to control in the recurrence free survival of Dukes B patients [1]. This initial investigation has been extended by two new studies where role of the microsatellite status and immune infiltrates of the tumors have been analyzed [2,3].

Active specific immunotherapy (ASI) is one of the first cellular immunotherapeutic strategies used in the clinic. An autologous tumor cell-BCG vaccine has been used to stimulate the immune system to fight against any leftover or recurring tumor cells. Using whole autologous tumor cells ensures the presence of all possible tumor associated antigens (TAA) in a patient specific manner [1]. However, most of the peptides present in the tumor cells are derived from 'normal' self proteins, not necessarily overexpressed by the tumor. Even though most proteins present in the ASI-vaccine are not specific for the tumor, it could be a good way to generally boost the immune cells in the tumor microenvironment.

Microsatellite status of colorectal patients

When the results of the ASI trial were first analyzed, no distinction was made between tumors that are microsatellite instable (MSI) and microsatellite stable (MSS). Now MSI tumors are considered a different group of tumors, with a better prognosis for the patients and should be treated differently. We found that patients with MSI tumors did not benefit from ASI therapy. In part this could be because the therapeutic window is very small for these patients, since their prognosis was already very good, even after a follow-up period of 15-years. This could be due to the already relatively active anti-tumor immune response, compared to the immune response of patients with MSS tumors. Others and we found a higher immune infiltrate in the tumor beds of MSI tumors compared to MSS tumors [2-5] . MSI tumors can present neo-antigens; these are tumor specific antigens formed by frame shift mutations, and could be responsible for the presence of a higher immune infiltrate [6]. MSS tumors do not (or hardly) express neo-antigens; still these tumors can have high immune infiltrates comparable to the immune infiltrates of MSI tumors. The disease specific survival and recurrence free survival for patients with MSS tumors and a high infiltrate can be significantly improved by ASI therapy [3].

The high immune infiltrates of MSI tumors seem to provide patients with these types of tumors with a good prognosis. In order for the immune infiltrates to have an anti-tumor effect it is important that the tumor cells do not loose their antigen presenting capacities. Unfortunately, due to the increased mutation rate of MSI tumors, errors start to occur in the class I and II presentation of these tumors, resulting in a lack of recognition by CD8+ and CD4+ T cells [7-9]. These patients may than benefit more from therapies employing NK or NKT cells [10].

Immunoscore

The prognostic value of tumor infiltrating lymphocytes has been investigated extensively for CRC patients [11-18]. Galon et al. have proposed using the number of TIL as an alternative classification system to determine prognosis; the immunoscore. The current focus of the immunoscore is on the presence of CD3+ and CD8+ cells in the tumor microenvi-

ronment of CRC patients. To implement this method worldwide it should be possible for hospitals around the world to perform these analyses, which entails automatic quantification of these cells in specific parts of the tumor tissue. The CD3+ and CD8+ cells can be either in the tumor margin, tumor stroma or tumor beds. While Galon et al. analyzed infiltrating cells in the tumor margin (or invasive margin) and the centre of the tumor [18,19], we and others analyzed the infiltrating cells in the tumor beds and the tumor stroma [3,4] . Although both methods show potential to be used as prognostic tool, there should first be consensus on how to perform the analyses with the strongest result. Furthermore, rather than the immunoscore being the sole prognostic marker it should be considered to use other tools as well. The UICC/TNM classification system together with microsatellite status with addition of the immunoscore could provide an accurate prognosis for CRC patients.

Furthermore the immunoscore can be of value as a predictive tool. We investigated the correlation between the presence of immune infiltrate in CRC patients and response to ASI therapy. We found that high numbers of stromal CD3+ and CD8+ cells are predictive for an improved response to ASI therapy [3]. It would be interesting to evaluate the predictive value of the immunoscore on more types of treatment.

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