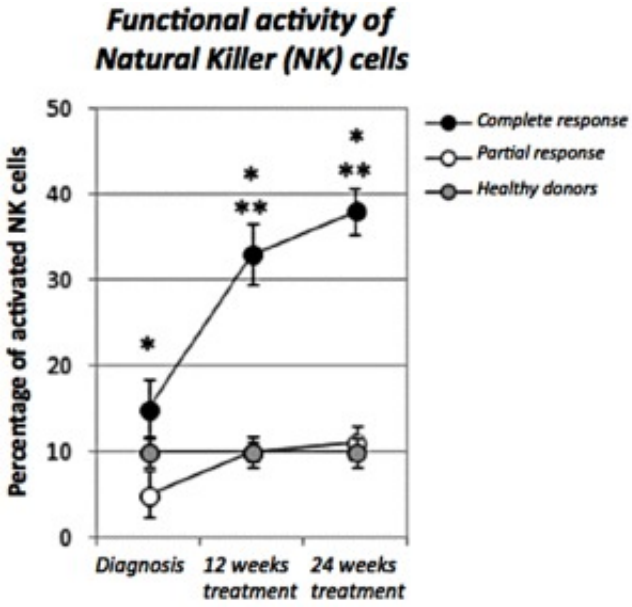
A functional immune system against cancer in breast cancer patients

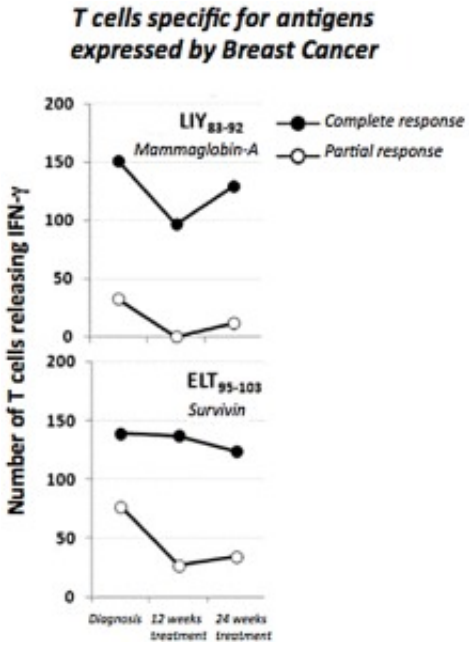
One of the hallmarks of cancer development is the ability of tumor cells to evade the recognition by the host immune system. However, the presence of immune responses against cancer is frequently observed in cancer patients. The contribution of these responses may favor a better outcome after therapy in particular when using drugs acting through mechanisms that involve the immune system. In this context, we characterized at diagnosis the immune profile of patients affected by a particular type of breast cancer, expressing high levels of the receptor HER2 and associated with a high proliferative rate. We interestingly noticed that the ability of their immune system to recognize tumor cells was less compromised than that of patients affected by a breast cancer expressing low or no levels of HER2. For this reason, we hypothesized that the monitoring of the immune profile during therapy could give us some interesting information about the ability of HER2-positive breast cancer patients to respond to treatment.



Before surgery these patients were treated with a combination of chemotherapy and an antibody, Trastuzumab, that targets the receptor HER2. This treatment induced a high rate of complete responses, namely the absence of tumor at the moment of surgery, and in the majority of patients at least a partial response (i.e. the reduction of tumor mass before surgery). Both Trastuzumab and the chemotherapeutic used in combination (Taxol) act through mechanisms involving the immune system. At diagnosis and during therapy we investigated the presence of different immune cells and their functional activity through the collection of serial blood samples.

The immune response against tumor is complex and involves both the innate and the adaptive compartment of the immune system. Within the innate compartment we studied the role of Natural

Killer (NK) cells, which are involved in one of the mechanisms of action of Trastuzumab. This antibody favors the killing of tumor cell expressing HER2 by NK cells through a mechanism called antibody-dependent cell cytotoxicity. In our study we noticed that the functional activity of NK cells improved after therapy only in those patients showing a complete response.



We also explored the adaptive compartment of the immune system. In particular, we quantified the number of lymphocytes T able to recognize proteins (antigens) usually expressed by tumor cells, as for example HER2. We selected antigens associated with breast cancer, stimulated T cells obtained from patients, and measured the release of a molecule called Interferon gamma (IFN-g), which causes the death of tumor cells. We observed that in patients reaching a complete response after therapy, the numbers of T cells recognizing 2 particular antigens, survivin and mammaglobin-A, were always higher that those observed in patients with a partial response. Since we observed the prevalence of responses against these antigens already at diagnosis, this feature may become a predictive marker of complete response to treatment.

Finally, we investigated the presence of a cell subset, called regulatory T cells, which suppresses the activity of anti-tumor T cells. We noticed that the number of regulatory T cells tended to increase in patients irrespective of the response to therapy. The enhancement of regulatory T cells might inhibit the boosting of T cells able to recognize tumor cells.

The preliminary results obtained so far lay the foundations for further studies aimed at finding biomarkers within the immune system components that could predict a better response to therapy. Hopefully, these findings may help clinicians to design therapeutic schedules reducing the number of regulatory T cells and exploiting the ability of patients' own immune system to fight cancer.

Publication

Improved Natural Killer cell activity and retained anti-tumor CD8(+) T cell responses contribute to the induction of a pathological complete response in HER2-positive breast cancer patients undergoing neoadjuvant chemotherapy.
Muraro E, Comaro E, Talamini R, Turchet E, Miolo G, Scalone S, Militello L, Lombardi D, Spazzapan S, Perin T, Massarut S, Crivellari D, Dolcetti R, Martorelli D
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