Immunomodulation induced by Stereotactic Ablative Radiotherapy (SABR) in Oligometastatic Breast Cancer Patients as a source of predictive biomarkers

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Background

- Improvements in the early detection of distant disease allow the diagnosis of isolated metastases, a clinical condition defined as oligometastatic.
- Stereotactic Ablative Radiotherapy (SABR) is a novel technique based on the delivery of very high radiation doses to the lesions.
- In oligometastatic lung cancer patients, the use of SABR favors the local control of the treated lesions minimizing normal tissue damage.
- A spontaneous distant tumor regression after SABR was documented in lung cancer, suggesting a specific involvement of the anti-tumor immune response.

- SABR may contribute to break local tolerance and release tumor-associated antigens (TAAs), improving host anti-tumor immunity.
- Spontaneous anti-tumor CD8+ T cell responses against several TAAs have been described in Breast Cancer (BC) patients.

Aim of the study

SABR could induce a benefit in oligometastatic BC patients maybe involving host immune system. We thus intend to perform a careful immunomonitoring of oligometastatic BC patients treated with SABR.

TO EVALUATE SABR EFFECTS ON HOST ANTI-TUMOR IMMUNE RESPONSES

with particular attention to patients concomitantly treated with drugs acting through immune-modulating mechanisms, as Trastuzumab.

Study design

- Patient enrolment
  - ≤ 6 metastatic lesions (diagnosed by FDG-PET/CT)
  - controlled loco-regional disease
  - no brain metastases

- Follow up
  - Possible concomitant therapy:
    - hormonal-therapy and/or chemotherapies
    - steroids
    - Trastuzumab

Diagnosis

24th after the first SABR fraction
1 month after SABR
2 months after SABR

Patients’ characteristics

<table>
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<tr>
<th>N</th>
<th>Group</th>
<th>Site</th>
<th>Treatment</th>
<th>Disease status</th>
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Sequences of selected epitopes

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</table>

Decreased B cells and increased CD56bright NK cells percentage after SABR

Methods. Analysis by flow cytometry of:
- T and B lymphocytes
- NK cells
- regulatory T cells
- myeloid-derived suppressor cells

Survivin-derived epitope-specific T cells

Survivin-derived epitope-specific T cells

Increased Trastuzumab ADCC efficiency 24h after SABR

Methods. In vitro CalcuSyn-based assay to evaluate Trastuzumab-mediated ADCC using:
- HER2-positive MDA-MB-435 cell line as target
- 20 ng/ml Trastuzumab
- patient’s antibodies as effectors
- normalization of lysis percentages to 10,000 NK

Conclusions

- SABR treatment induced several immune-modulating effects in oligometastatic BC patients:
  - increased survivin-specific CD8+ T cells numbers
  - enhanced polyfunctional HER2-specific CD8+ T cells
  - reduced B cells and increased CD56bright NK cells (%
  - improved Trastuzumab ADCC activity
  - restored serum IL-8 levels (in comparison with healthy donors)

- FUTURE PERSPECTIVES
  - We intend to complete the study through:
    - the implementation of patients’ follow-up (total n=30)
    - the immunomonitoring during further follow-up (n=30 over 3 years)
    - the evaluation of host anti-tumor immune response contribution to the induction of a clinical response to SABR (at 3 years follow-up)

References