Plasma collected during radiotherapy in triple-negative breast cancer patient stimulates development of lung metastases in a mouse model

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Abstract

Purpose: Recurrence within the first three years after treatment occurs in ~30% of patients with early stages triple-negative breast cancer (TNBC). However, there is no biomarker to identify them. Radiotherapy (RT) triggers an inflammation in all patients. Some of these inflammatory cytokines promote cancer cell invasion, increase the number of circulating tumor cells and stimulates metastasis development. The purpose of this study is to determine if plasma collected during RT could be used to identify TNBC patients at high risk of recurrence.

Materials and Methods: Plasmas were collected in TNBC patients before RT and after the 4th radiation fraction (plasma during RT). The increase in inflammatory cytokines was analyzed by ELISA type test. The plasmas were incubated with TNBC MDA-MB-231 (human) and D2A1 (mouse) cells in order to determine which plasmas collected during RT increase their invasion capacity in vitro, as well as the formation of metastases in mice.

Results: Our preliminary results obtained from 5 TNBC patients demonstrated that RT increased the plasma level of the cytokines IL-1β, IL-5 and IL-6 only in the patient whose cancer recurred within the first 9 months following treatment. Only plasma from this patient collected during RT increased the invasiveness of TNBC cells in vitro and the formation of metastases in an animal model. The formation of metastasis was completely blocked by adding the cyclooxygenase-2 (COX-2) inhibitor Celecoxib to this plasma collected during RT.

Conclusions: We would like to continue recruiting TNBC patients in order to confirm that plasma collected during RT could identify patients at high risk for recurrence.
IDENTIFICATION OF THE SUBGROUP OF PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER AT HIGH RISK OF RELAPSE: PILOT STUDY
(Plasma collected during radiotherapy in triple-negative breast cancer patient stimulates development of lung metastases in a mouse model)

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INTRODUCTION

Recent studies reveal that ∼15% of patients with early-stage triple-negative breast cancer (TNBC) included in clinical trials fail to benefit from chemotherapy. TNBC patients with local-regional recurrence or breast-conserving therapy with or without adjuvant radiation therapy are at risk of relapse. However, the identification of a subgroup of TNBC patients who would benefit from systemic treatment is challenging. Currently, the absence of reliable markers at diagnosis or after recurrence limits the potential for early intervention. The identification of novel predictive and/or prognostic biomarkers could improve the accuracy of patient selection for systemic therapy. In this study, we evaluated the clinical relevance of plasma collected from patients with TNBC undergoing radiotherapy during adjuvant therapy. The aim of this pilot study was to determine if plasma from patients with TNBC undergoing adjuvant radiotherapy could be used for identification of TNBC patients at high risk of recurrence.

OBJECTIVES

1. Determine whether a profile of cytokines induced by radiotherapy could identify TNBC patients at high risk of recurrence.
2. Evaluate the abilities of cytokines to predict radiotherapy-induced metastasis formation.
3. Evaluate the ability of cytokines to predict radiotherapy-induced lung metastasis formation.

METHOD

TNBC Patient Selection Criteria

- Histological confirmed TNBC status
- Primary tumor surgically removed and negative margins
- Regional lymph nodes positive
- No evidence of distant metastases at diagnosis as determined by FDG-PET scan or by CT scan with breast scan
- Radiotherapy, after chemotherapy and surgery
- Few patients enrolled up to now

RESULTS

Phenotypic characterization

Cytokine quantification

Cancer cell invasion assay

Metastasis formation assay

Expression of the receptors (GFR) to EPL and cell adhesion protein EPCAM and VCAM-1

EPL, EPL, and VCAM-1 expression was decreased in the EPCAM and VCAM-1 assays. Despite high EPCAM and VCAM-1 expression, few patients exhibited metastasis.

CONCLUSION

In conclusion, plasma collected during radiotherapy from patients with TNBC could be used as a tool for early prediction of cancer cell invasion and metastasis formation. This pilot study suggests that plasma collected during radiotherapy could be a powerful tool for the identification of patients at high risk of recurrence, allowing for early intervention with systemic therapy.