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Relevance of B and NK cells in the correlation between radiation-induced lymphocyte apoptosis (RILA) and normal-tissue late toxicity after radiotherapy

Autor: Yingying Zhang
Institut / Klinik: Klinik für Strahlentherapie und Radioonkologie
Doktorvater: Prof. Dr. M. Veldwijk

Breast cancer constitutes 1 in 4 cancer cases and 1 in 6 cancer-related deaths in women, thereby being the leading cause of morbidity and mortality. Improvements in the treatment of breast cancer have resulted in a rise in the number of long-term survivors. Therefore, the effect of therapy-induced late effects on quality of life becomes of increasing relevance and with this, predictive assays for these effects. Radiation-induced lymphocyte apoptosis (RILA) after in vitro irradiation of T cells is a promising predictive assay for the late effects of radiotherapy (RT). Several publications have discussed the potential relevance of B and NK cell populations for prediction assays. Yet, in a previous study, NK cells proved to be extremely radiosensitive. The aim of this study was to determine the potential association between RILA in B cells and late effects of RT as well as to further investigate the feasibility of NK cells for use in the RILA assay. In addition, the relevance of other risk factors, such as age, BMI, smoking, hypertension, and total dose of irradiation, were also investigated. In the observed German study cohort with 252 breast cancer patients, 10 years after the radiotherapy, 61 (25.2%) and 12 (4.8%) experienced grade 2 and 3 fibrosis, respectively. Grade 2 and 3 telangiectasia were observed in 15 (6.0%) and 6 (2.4%) patients, respectively. The cumulative incidences of high-grade fibrosis (grade 2+3) and telangiectasia (grade 2+3) at 10-year follow-up were distributed evenly in our three RILA groups. Unlike previous observed with CD4 lymphocyte RILA, no significant difference in RILA in B lymphocytes was observed between patients with and without fibrosis ($p=0.78$) or telangiectasia ($p = 0.66$). Additionally, the location of the fibrosis, inside the surgical area: $p = 0.34$ or outside the surgical area: $p = 0.68$, also didn't show any significant difference. Besides RILA scores in B lymphocytes, also other potential factors, including age, obesity, smoking, hypertension, and total dose of irradiation were investigated. Age and smoking were not significantly associated with radiation-induced acute toxicities, fibrosis and telangiectasia risk at 10 years follow-up. However, a significant relationship was found between BMI and acute toxicities ($P = 0.007$), fibrosis ($P = 0.004$) and telangiectasia ($P = 0.032$) at 10 years follow-up. Radiation therapy with ≥ 60 Gy was found to significantly increase the risk of acute toxicities ($P = 0.017$) and telangiectasia ($P = 0.038$) at 10-year follow-up, but had no significant effect on fibrosis ($P = 0.658$).

To counter the high radiosensitivity of NK cells, which was previously observed, the effect of incubation time after in vitro irradiation (4h-48h) and/or the irradiation dose (0.25 Gy- 3.0 Gy) on apoptosis was observed. A significant, dose-dependent increase in apoptosis was observed more than 16 hours after irradiation, yet this also resulted in a dramatic decline in the total number of NK cells after doses ≥ 1 Gy, thereby making NK cells unsuitable as a potential predictor using the RILA assay.

In conclusion, no significant association between B cell RILA and radiation-induced late toxicities, including fibrosis and telangiectasia, was observed. Other potential clinical factors, such as BMI and dose of irradiation did correlate and may therefore be taken into account. The NK cell population seems to be unsuitable for the RILA assay, as no experimental conditions (irradiation dose, incubation time) were observed in which sufficient cells survived for a reliable determination of RILA. Hence, the relevance of NK cells in the development of RT-induced late normal-tissue reactions remains unclear.