Individual ADCC capability predicts treatment outcome under cetuximab-based therapy in head and neck cancer?

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Background

Cetuximab is a IgG1 monoclonal antibody against epidermal growth factor receptor (EGFR) used for the treatment of local advanced-head and neck squamous cell carcinoma (LA-HNSCC). The working mechanism of cetuximab includes the ability to develop antibody-dependent cell-mediated cytotoxicity (ADCC), triggered by the interaction of the Fc portion of the antibody with the Fc receptor on the immune cells, mainly on Natural Killer (NK) cells. Invariant NKT (iNKT) cells play an important role in the activation of immune system, including NK cells, and their deficiency is related to poor clinical outcome in LA-HNSCC.

The aim of this study was to investigate the predictive role of ADCC and iNKT in LA-HNSCC patients treated with cetuximab-based therapy.

Material and methods

Patients

There were 28 patients treated at the S. Croce & Carlo Carlei Teaching Hospital (Cuneo, Italy) between 2007 and 2015. All patients were treated with curative intent by chemoradiotherapy (CRT) associated with cetuximab. The median age was 65 years (range 43-87 years). 22 patients were males and 6 females. 16 patients expressed high EGFR level (3+) and 12 low EGFR level (0, 1+). Methods

Peripheral blood samples were collected at the start of therapy. Intracellular ADCC was evaluated from ex vivo NK-dependent activity measuring CD107a release through the Cytotox 96 non radioactive cytotoxicity assay, previously standardized in our laboratory. EGFR tumoral expression was analysis by immunohistochemistry. NK cells were defined as CD3-/CD56+ and iNKT cells by co-expression of CD3, TCR Vα24, TCR Vβ11.

Statistics

Statistical analyses were performed using the GraphPad Prism 5 (San Diego, CA, USA) and SPSS version 19 (SPSS, Chicago, IL) programs. OS analyses were based on the time from treatment start to death or last contact in which the survivors were censored. OS was calculated using the Kaplan-Meier method with log-rank test for statistical significance. A p-value <0.05 was considered statistically significant.

Results

We did not observe a statistical correlation between EGFR expression and OS in patients treated with CRT+cetuximab (p=0.123). In order to investigate a possible role of ADCC in predicting cetuximab response, we studied the correlation between ADCC and OS in our cohort of patients (Figure 1). We observed that patients with high ADCC (>median value=62.6%) at baseline level showed a significant increased OS compared to patients with low ADCC (<median value=38.6%) (p=0.0033). The same analysis performed in a control group (15 patients treated with CRT but without cetuximab) showed that ADCC has no impact on OS when patients were treated without cetuximab (p=0.9191, data not shown). Moreover, we observed a correlation between high ADCC and response rate (Figure 2). By univariate analysis on OS (Table 1), we observed higher ADCC activity, tumor size and HPV status as significant prognostic indicators. According to multivariate log-rank analysis, only ADCC remained a significant predictor for OS (p=0.03).

Conclusions

ADCC has a strong predictive value in cetuximab-treated LA-HNSCC patients. High tumoral EGFR expression and high ADCC confer a particularly long overall survival and suggest to combine this two biomarkers in order to predict clinical outcome in cetuximab-treated LA-HNSCC patients.

Bibliography


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