Potentiation of the antitumor effect of electrochemotherapy with bleomycin, cisplatin or oxaliplatin by immunostimulation with IL-12 gene electrotransfer depends on the tumor immune status

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The therapeutic effectiveness of electrochemotherapy (ECT) in the clinics is up to 90% of local tumor control; however, a systemic antitumor effect (abscopal effect) has not yet been observed. The aim of the study was to test a new combined therapy including ECT with cisplatin, bleomycin or oxaliplatin and gene electrotransfer (GET) of plasmid encoding interleukin-12 (IL-12) in three immunologically different tumors. We hypothesized that in the combination, IL-12 boosts the in situ vaccination effect of ECT by recruiting effector immune cells. A malignant melanoma (B16F10), mammary carcinoma (4T1) and colon carcinoma (CT26) were treated (U34401-1/2015/7). Growth of primary treated tumors and of distant untreated tumors in a dual-flank model mimicking systemic disease was followed. After the therapy, cytometric and immunohistochemical analysis were performed to detect immunologically important biomarkers. In poorly immunogenic B16F10 melanoma, IL-12 potentiated the antitumor effect of ECT with biologically equivalent low doses of cisplatin, oxaliplatin or bleomycin. However, we observed the most pronounced potentiation after ECT with cisplatin, resulting in 38% of complete responses as well as an abscopal effect. The antitumor effectiveness of this treatment combination could be ascribed to the induction of the local and systemic immune responses. Namely, infiltration of granzyme B positive effector immune cells was observed in both, primary and distant tumors. Furthermore, we observed better responsiveness to ECT in more immunogenic 4T1 and CT26 tumors, where the addition of GET led to the lowest potentiation. To conclude, we showed that IL-12 boosts the effect of ECT by recruiting effector immune cells in poorly immunogenic melanoma. Effectiveness of the tested treatment combinations depends on the immunological status of the tumor; ECT was more effective in more immunogenic tumors but the contribution of GET was higher in less immunogenic tumors.