

Combined treatment of advanced head and neck cancer with radiotherapy and cyclooxygenase-2 inhibitors (phase I study)

This paper describes the course and presents the outcomes of a original phase I study of combined treatment of advanced head and neck cancer using standard radiotherapeutic technique and COX2 inhibitor (Celebrex) as a potentiating agent. The primary goal of the study was identifying of the maximum tolerated dose of Celebrex for the purpose of further clinical investigation.

In the theoretical introduction I present data on the incidence and mortality of HaN cancer worldwide and in the Czech republic, further preclinical data justifying use of Celebrex in combined treatment with radiotherapy. Special emphasis was put on presentation of local data systematically gained in Clinic of Oncology in Ostrava where this study has been conducted. These data include an overview of incidence, mortality, therapeutic methods and treatment toxicity profiles. Since the phase I study as such does not include comparison with control patient group, it is necessary to be aware of local standards. This is the background to establish inclusion criteria for patient recruitment, toxicity evaluation and setting maximum tolerance dose criteria.

This study furthermore investigates expression of COX2 in tumor tissue and serum VEGF level as a potential marker of vasculogenesis or its drop corresponding to tumor regression respectively.

This project included preparation of study, securing financial support, obtaining ethical committee approval, further the recruitment of patients, conducting radiotherapy, distribution of study medication, processing of biopsy tumor tissue, processing of serum specimens, follow-up of patients, collecting and statistical analysis of data.

Patient recruitment followed predefined inclusion criteria. The main criterion was a presence of locally advanced not operated squamous cell carcinoma. All together 32 subject were included. All patients were irradiated up to 72Gy with concomitant boost technique and all patients completed prescribed therapy. Patients were administered Celebrex during the whole course of radiotherapy, including weekend days. The dose of Celebrex was escalated by doubling among study cohorts. The starting dose was 400 mg per day, the highest administered dose was 1600 mg per day. The maximum tolerated dose of Celebrex that did not generate any extra toxicity was established at 1200mg per day. This dose was higher than any other presented in literature since the published MTD was 800 mg per day.

Serum VEGF levels were tested with ELISA. Samples were obtained before treatment start, in the middle of treatment course, at the end of treatment and 6 weeks after completion of treatment. Statistically significant drop of VEGF level was demonstrated between the levels on treatment start and in 6-week follow-up. The outcome was further correlated with initial COX2 expression in tumor tissue. The COX2 expression was evaluated with semiquantitative immunohistochemistry methods. Expression of COX2 over 50% was considered high, below or equal 50% reckoned as low. The analysis has shown that VEGF level drop was present only in patient with high COX2 expression in their tumors. This assessment was conducted in clinical setting, therefore it does not explain cellular or molecular basis of this phenomenon, nonetheless it proves the interconnection of COX2 and VEGF pathways.

This project brought few new findings; maximum tolerance dose of Celecoxib in patients with locally advanced head and neck cancer treated with radiotherapy with curative intent is 1200 mg per day. Further, in patients with tumors expressing COX2 in more than 50% of tumor cell a statistically significant drop of VEGF serum level can be observed in follow-up.