Göteborg, 2021

Aspects of Chemotherapy in Prostate Cancer

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, Akademicum, den 5 november 2021, klockan 09:00

av Åsa Jellvert, leg läkare

Fakultetsopponent:
Professor Jan Oldenburg
Akershus universitetssykehus, Oslo, Norge

Avhandlingen baseras på följande delarbeten

I. Castration is a prerequisite for the inhibitory effect of metronomic chemotherapy on the growth of experimental castration-resistant prostate cancer **Jellvert Å**, Åhs D, Olausson J, Lissbrant IF, Damber JE, Welén K. ACTA Oncologica 2018; 557: 895-901

II. Biomarkers for prediction of response and survival of chemotherapy in patients with advanced prostate cancer. **Jellvert Å**, Larsson K, Schnedl L, Damber JE, Gasi Tandefelt D* Welén K*. Manuscript

III. Progression-free survival advantage of docetaxel plus bicalutamide versus bicalutamide alone for non-metastatic prostate cancer, a Scandinavian Prostate Cancer Group Study, SPCG-14. Josefsson A*, **Jellvert Å***, Holmberg E, Brasso K, Meidahl Petersen P, Aaltomaa S, Luukkaa M, Verhagen P, de Wit R, Ahlgren G, André O, Castellanos E, Seke M, Widmark A, Turesson I*, Damber JE*. Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Aspects of Chemotherapy in Prostate Cancer

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Abstract

Since 2004 chemotherapy has been a part of standard of care in prostate cancer (PC) and improved symptom control and survival has been demonstrated in metastatic castration-resistant PC. Whether docetaxel has benefits in earlier stages of PC is currently under investigation. Metronomic chemotherapy (MC) is used in the clinic mostly for elderly and fragile patients due to the relatively mild side effects, but its effects have not been confirmed in prospective randomized trials of sufficient size. The MC mechanism of action is not fully understood. For chemotherapy treatment in general, there is a lack of predictive and prognostic markers.

In an animal model we showed that chemotherapy administered in a metronomic schedule to castrated animals had equal effect as conventionally administered chemotherapy given at the maximum tolerated dose. We explored the possibility of an anti-angiogenic mechanism of action. Induction of the anti-angiogenic factor TSP-1 mRNA indicated a possible anti-angiogenic effect, but this was not confirmed in assessment of microvessel density.

In two cohorts of patients treated with docetaxel or metronomic cyclophosphamide, we evaluated predictive and prognostic liquid biomarkers and found that hemoglobin was predictive for docetaxel treatment and that circulating cell-free DNA was prognostic for MC treatment. Platelet-derived proteins as potential liquid biomarkers in the circulation were evaluated and shown to be promising. Some proteins showed prognostic value in advanced PC, and a few showed predictive value.

Chemotherapy was evaluated in early stages of PC in a randomized phase 3 study. For patients with recurrent disease after curative treatment or patients with high-risk PC not suitable for curative treatment, docetaxel combined with antiandrogen therapy showed advantage in progression-free survival compared to antiandrogen therapy alone.

Keywords: prostate cancer, CRPC, chemotherapy, metronomic, prognostic, predictive, biomarkers

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