Less dexamethasone when administering docetaxel

The Dutch NVMO Committee for Sustainability and Efficiency has formulated recommendations to reduce the amount of docetaxel required when administering docetaxel. The goal is to make the treatment more patient-friendly and more cost-effective while reducing use of resources and thus environmental impact.

Introduction

Approximately 4,500 patients in the Netherlands undergo treatment with docetaxel annually for various types of tumours. (1) Dexamethasone, a potent corticosteroid, is administered prior to and after this treatment to reduce the risk of docetaxel-related side effects such as hypersensitivity reactions (HSRs) and fluid retention. The medication leaflet advises a dosage of 16 mg of dexamethasone per day (8 mg twice daily) for three days, starting one day before the docetaxel treatment (a total of 48 mg of dexamethasone per cycle) for the treatment of breast, non-small cell lung, stomach, and head and neck cancer. For prostate cancer treatment which is associated with daily use of prednisone or prednisolone, the recommended premedication dose is 8 mg of dexamethasone orally, taken 12 hours, 3 hours, and 1 hour before docetaxel (a total of 24 mg of dexamethasone per cycle). (2) Especially in case of weekly treatment with docetaxel, the dexamethasone doses are tremendous.

The optimal dosing of dexamethasone has been a subject of debate for years, particularly due to the limited evidence for the current high dosages. (3) High doses of dexamethasone can cause severe side effects such as hyperglycemia, immunosuppression with increased susceptibility to infections, mood and sleep disturbances, and weight gain, all negatively affecting the quality of life of patients. (4) This raises the question of whether the current high doses of dexamethasone can be reduced to improve quality of life outcomes without increasing side effects such as HSR and fluid retention.

Literature Review on the Effectiveness of Lower Dexamethasone Doses

Various studies suggest that lower doses of dexamethasone may be as effective as higher doses in preventing docetaxel-related HSRs and fluid retention (see Table 1). Kang et al. (2017) investigated this in a retrospective study (n=206) by comparing two dosing regimens of dexamethasone in patients with lung, esophageal, and breast cancer treated with docetaxel used as monotherapy or in combination therapy. The control group received 10 mg of dexamethasone intravenously, followed by 4 mg orally twice daily for two days, while the experimental group received a single intravenous dose of 10 mg. Both groups showed a similar incidence of fluid retention (0.9% vs. 0) and HSRs (8.3% vs. 8.2%), with a significantly lower incidence of infections in the lower total dose dexamethasone group ($p = 0.020$, OR = 0.408, 95% CI: 0.0190–0.0879). (5)

Lansinger et al. (2021) conducted a large retrospective analysis (n=3181) on the relationship between the administration route and dosing of dexamethasone and the occurrence of HSRs with taxanes (both paclitaxel and docetaxel). This study found no association between the

dosage and administration route of dexamethasone and the occurrence of HSRs with docetaxel (n=1381). Based on this, the authors suggest that doses above a single dose of 10 mg (intravenous or oral) seem to have no additional benefit. (6)

In an RCT (n=162) by Zhang et al. (2021), a lower dose of dexamethasone appeared to be as effective as a higher dose in preventing HSRs and docetaxel-related side effects in patients treated with weekly 25 mg/m2 or tri-weekly 75 mg/m2 docetaxel. In this study, the experimental group received 4.5 mg of oral dexamethasone once daily, and the control group received 8 mg orally twice daily, both for three days. No significant difference in the occurrence of HSRs was found (11.1% vs. 9.7%). There were also no significant differences in the occurrence of other side effects such as fluid retention and nausea (Table 1). (7)

In the retrospective study by Chen et al. (2016) (n=336), the effectiveness and safety of different dexamethasone dosages were examined in patients with head and neck tumors treated with a combination of docetaxel and cisplatin, with some cases also included fluorouracil. The total dexamethasone doses per cycle ranged from 45 mg (n=30), 32 mg (n=20), 16 mg (n=20) to 11 mg (n=266). The study showed that HSRs ≥grade 3 were rare, with only 3 occurrences (1.1%) in the 11 mg group and none in the higher dose groups. The occurrence of grade ≥3 edema was 1/30 in the 45 mg group, none in the 32 mg group, 1/20 in the 16 mg group, and 4/266 in the 11 mg group. (8)

Finally, Luchtenberg et al. (2023) in the Netherlands investigated the effect of reducing the dexamethasone dose with docetaxel in a dose-escalation phase 1 study in 39 patients with prostate cancer or breast cancer. In successive cohorts, a decreasing dexamethasone dose was administered. If no grade III/IV HSR or fluid retention occurred in six patients within one cohort, the patients in the next cohort were treated with a lower dexamethasone dose level. In patients with prostate cancer (n=25), the dexamethasone dose was reduced to a single dose of 4 mg on the day of docetaxel administration; in patients with breast cancer (n=14), the dose was reduced from 3 days of 8 mg twice daily to a regimen of 3 days with 4 mg - 8 mg - 4 mg once daily, after which no further reduction was tested. None of the 39 patients developed severe grade III/IV fluid retention or HSR. One patient (2.6%) had a grade 1 HSR, and six patients (15.4%) had grade I. (3)

Current Practice

In Dutch hospitals, there are significant variations in the dexamethasone dosages used around docetaxel treatments. Some centers, such as the Maxima Medical Center and Isala Zwolle, already use a lower single dose of 4 mg dexamethasone orally, administered at least 30 minutes before the docetaxel treatment. According to this protocol, several hundred patients have already been treated in these centers without problems, with the perception that patients experience fewer side effects without an increase in HSR and edema.

Recommendation of the Dutch Society of Medical Oncology

We advise reviewing the dexamethasone dosage given before and after docetaxel treatments, given the side effects and the lack of convincing evidence for the current high dexamethasone dosages. Although there are only a limited number of studies available and

a lack of extensive RCTs on this topic, the existing literature and practical experience in two large hospitals in the Netherlands suggest that a lower dose of dexamethasone can be safe and effective. There is no clear preferred dosage to be identified. Given the lack of evidence for the high dexamethasone dosage and its severe side effects, combined with the aforementioned studies and extensive practical experience, the committee, based on expert opinion/best practice data, recommends lowering the dexamethasone dosage in docetaxel treatments to the lowest investigated variant. Based on the described literature, 8 mg dexamethasone once is a safe dosage. Based on practical experience, a single oral dose of 4 mg, administered at least 30 minutes before treatment with docetaxel, can suffice as long as no other highly emetogenic oncolytics such as cisplatin are given simultaneously.

Table 1: **Overview of characteristics and outcomes of studies with lower dexamethasone dosages around docetaxel administration.**

Study	**Study type**	**Population**	**Dose dexamethason**	**Outcomes (control vs experimental group)**
Kang et al. (2017)	Retro-spective (n=206)	Docetaxel mono- and combination therapy lung, esophageal and breast cancer	Control group: 10 mg IV + 4 mg oral bid for 2 days; Experimental: 10 mg IV once only	HSR: 8.3% vs 8.2% (p=0.998); Fluid retention 0.9% vs. 0% (p=0.344); Infections: 23.9% vs 11.3% (OR = 0.408, p = 0.020)
Lansinger et al. (2021)	Retro-spective (n=3181)	Patients treated with paclitaxel or docetaxel)	Variable (intravenous or oral, 0 till >20 mg)	Neither dexamethasone dose nor route correlated with subsequent HSRs
Zhang et al. (2021)	RCT (n=162)	25 mg/m2 or 75 mg/m2 docetaxel (tumour type not specified)	Control group: 8 mg bid for 3 days; Experimental: 4.5 mg once a day for 3 days	HSRs 9.7% vs 11.1%; Fluid retention 14.3% vs 10.1% Q1W and 11.1% vs 4.5% Q3W Nausea 22.9% vs 27.5% Q1W and 27.8% vs 22.7% Q3W
Chen et al. (2016)	Obser-vational (n=336)	Head and Neck Cancer docetaxel with cisplatin and fluorouracil	Variable dosing: 45 mg (n=30), 32 mg (n=20), 16 mg (n=20) en 11 mg (n=266)	HSR-grade ≥3: 3/266 (1.1%) in 11 mg group, no HSRs in other dose groups. Edema graad ≥3: 1/30, 0/20, 1/20, 4/266 in 45 mg, 32 mg, 16 mg, 11 mg group respectively
Luchtenberg et al. (2023)	Dosis-de-escalation fase-1 study (n=39)	Prostate cancer Breast cancer	Minimal dose used in prostate cancer: 4 mg only once; breast cancer: 4 mg - 8 mg - 4 mg once daily for 3 days	No grade III/IV fluid retention or HSR; 2.6% grade 1 HSR; 15.4% grade I or II edema; Nausea: 5/12, 5/13, 2/14 patiënten in dosiscohort 1, 2, 3 respectively. No differences in QoL between dose cohorts

About the Authors:

The committee “sustainability and efficiency” of the Dutch Society of Medical Oncology (NVMO) was initiated in 2022. Their remit is to demonstrate that it is possible to increase both the sustainability as well as the efficiency of medical oncology care. The committee consists of medical oncologists and hospital pharmacists. They regularly publish specific guidelines and suggestions for daily practice based on both published literature and daily experience. All published guidelines are freely accessible at “https:www.nvmo.org/duurzaam-en-doelmatigheid/”

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