Premedication strategy for paclitaxel, still an unsolved question after 30 years

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SUMMARY

Background: For paclitaxel administered 3-weekly, the Food and Drug Administration recommends the use of premedication with dexamethasone 20 mg orally twelve and six hours prior to paclitaxel, histamine-1 and -2 antagonists 30-60 minutes prior to paclitaxel, to prevent hypersensitivity reactions. There are no guidelines for the use of premedication when paclitaxel is given weekly.

Material and methods: MEDLINE was searched using the keywords premedication, dexamethasone, paclitaxel and hypersensitivity in November 2016. Articles were surveyed for additional citations.

Results: We retrieved 28 papers, of which sixteen on prospective trials (four on weekly, nine on 3-weekly paclitaxel). Using a dexamethasone tapering regimen in patients without hypersensitivity reactions after the first weekly paclitaxel administration, hypersensitivity reactions were reported in 1.0%, 2.3% and 5.7% of patients. In five single arm studies, intravenous dexamethasone 20 mg was administered prior to 3-weekly paclitaxel. Hypersensitivity reaction rates varied between 0-15%. Hypersensitivity reaction rates in sequential cohorts, in a single centre, with an intravenous or oral dexamethasone regimen were 14.5% and 5.4%, respectively (p=0.07). In a randomised trial there was no significant difference between an intravenous and oral dexamethasone regimen prior to 3-weekly paclitaxel administration.

Conclusions: Tapering of dexamethasone or no premedication at all seems to be safe in patients without hypersensitivity reactions after the first weekly administration of paclitaxel. Substitution of oral dexamethasone by a single intravenous administration immediately prior to 3-weekly paclitaxel was associated with a higher risk of hypersensitivity reactions, until 17,9%.

(BELG J MED ONCOL 2017;11(2):46-55)

INTRODUCTION

Paclitaxel is a crude extract from the bark of the Pacific yew tree, *Taxus brevifolia*. It inhibits the disassembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation, causing mitotic block and cell death.[1]

Paclitaxel is widely used as a chemotherapeutic agent. It has been approved by the Food and Drug Administration (FDA) for the treatment of breast cancer, non-small cell lung cancers (NSCLC), advanced ovarian cancer and AIDS-related Kaposi's sarcoma.[2] It's also used (off-label) for head and neck cancer, small-cell lung cancer, upper gastro-intestinal adenocarcinoma, hormone-refractory prostate cancer, non-hodgkin lymphoma, urothelium transitional cell carcinoma, stage IIB-IV melanoma, advanced cervical cancer, metastatic penile cancer, soft tissue sarcoma, testicular germ cell tumours, thymic carcinoma and unknown primary adenocarcinoma.

Early phase I clinical trials were complicated by a high incidence of hypersensitivity reactions (HSR) occurring mostly during or immediately after the first administration.[3,4] Three different mechanisms may be responsible

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: corticosteroids, hypersensitivity reactions, paclitaxel, premedication.

for the acute HSR: complement activation induced by Cremophor EL, histamine release through a direct effect of paclitaxel on basophils and an IgE/IgG-mediated mechanism against the taxane moiety or the solvent.[2] The FDA recommends the use of premedication with dexamethasone 20 mg orally, twelve and six hours prior to paclitaxel, along with the oral (po) or intravenous (IV) administration of the histamine-1 (H1) antagonist and a histamine-2 (H2) antagonist 30-60 minutes prior to paclitaxel administration.[5] After the introduction of this premedication regimen, the incidence of the major HSR decreased from 25-30% to approximately 2-4%.[3,6] This premedication regimen is recommended for paclitaxel given every three weeks. Weekly administration has become standard-of-care for the treatment of breast cancer.[7] There are no guidelines regarding the optimal premedication regimen when paclitaxel is given weekly.[5] Weekly administration of the above mentioned premedication regimen exposes patients to a high dose of corticosteroids, potentially inducing unacceptable side effects including hypertension, hyperglycaemia, osteoporosis, altered mood, flushing, acne, insomnia, weight gain and cushingoid changes.[8] We therefore searched the literature for evidence on reduced steroid dosing prior to weekly and 3-weekly paclitaxel.

MATERIAL AND METHODS

MEDLINE was searched using the keywords premedication, dexamethasone, paclitaxel and hypersensitivity in November 2016. Articles were surveyed for additional citations.

RESULTS

Total search result abstracts
n = 124
↓
Papers after duplicate removed
n = 96
↓
Irrelevant articles by title and abstract
n = 75

Initial articles reviewed
n = 21
↓
Additional articles reviewed after reviewing references
n = 7

Total number of included studies
n = 28

WEEKLY PACLITAXEL

Braverman et al. designed a single centre prospective trial with a dexamethasone tapering regimen. One hundred and twenty-two breast cancer patients took 20 mg of dexamethasone orally twelve and eight hours prior to the first administration of paclitaxel. Patients without HSR received dexamethasone IV immediately prior to the next administrations of paclitaxel, with dose decrements, reaching 0 mg by the 9th administration (*Table 1*). Acute reactions were reported in seven (5,7%) patients. Four patients developed a HSR during the first and two during the second administration of paclitaxel. In only one patient (0,8%) tapering of the dexamethasone dose (10 mg) had begun.[9] Zidan et al. also prospectively studied a dexamethasone tapering premedication regimen. Only one patient (1%) had to stop therapy after four cycles of paclitaxel due to a HSR. They didn't specify the type of reaction.[10] In a very small phase I study, fifteen patients with advanced NSCLC received dexamethasone at varying doses from 16 mg until 2 mg in a tapering schedule. If the maximum tolerated dose was determined, the initial dexamethasone dose of 8 mg was tapered until 1 mg IV (*Table 1*).[11] The prevalence of HSR did not correlate with the paclitaxel dose and the dexamethasone dose reductions.[11]
In a prospective trial by Green et al., early stage breast cancer patients received twelve doses of weekly paclitaxel 80 mg/m^2.[12] Dexamethasone 10 mg was administered IV 30 minutes prior to administration of paclitaxel week 1-3. Before cycles 4-12, patients received dexamethasone 4 mg IV. In the event of an allergic reaction, diphenhydramine and/or cimetidine were added for subsequent doses of paclitaxel. Serious (grade 3) reactions were mentioned in 0,3% of patients.
A retrospective analysis by Quock et al. suggests that it is safe to stop all premedications (H1/H2 antagonists with dexamethasone 10 mg IV, 30 minutes prior to the first dose) if there is no HSR during or after the first weekly administration of paclitaxel. They reported no HSR.[13]
In a single centre cohort, 89 taxane-naïve patients with advanced NSCLC were treated with paclitaxel followed by gemcitabine on days 1, 8, and 15 4-weekly. Premedication consisted of prednisone 25 mg orally one day prior to the paclitaxel administration and hydrocortisone 250-500 mg plus chlorpheniramine 10 mg IV immediately before paclitaxel administration. Three (3,4%) patients got severe dyspnoea and bronchospasm, which was attributed to gemcitabine in one patient.[14]

TABLE 1. Weekly paclitaxel.

Trial	Study design	Paclitaxel schedule	Premedication corticosteroids	Premedication H1 and H2 blockers	N	No. cycles	No. patients	Percent patients
Braverman et al. 2005	Prospective	80-100 mg/m^2	* Cycle 1: dexamethasone 20 mg oral 12h and 08h** No reaction: * Cycle 2 dexamethasone 20 mg IV * Cycle 3 - 4 dexamethasone 10 mg IV * Cycle 5 - … dexamethasone IV 2 mg decrements until 0 mg	H1 blocker IV No reaction: * Cycle 5 - … H1 blocker oral	122	896	7	5,73%
Quock et al. 2002	Retrospective	50-90 mg/m^2	* Cycle 1 dexamethasone 10 mg IV * No reaction Cycle 2 - … no premedication	* H1/ H2 blockers IV * Cycle 2 - … no premedication	30	205	0	0%
Green et al. 2009	Prospective	80 mg/m^2	* Cycle 1 – 3 dexamethasone 10 mg IV * Cycle 4 – 12 dexamethasone 4 mg IV	H1/ H2 blockers IV, only by previous reaction	302		6	2,30%
Milani et al. 2007	Unclear	60-100 mg/m^2	prednisone 25 mg po day 0, hydrocortisone 250 – 500 mg IV day 1	H1 blocker IV	89	341	3	3,4%
Zidan et al. 2008	Prospective	60-80 mg/m^2	* Cycle 1: dexamethasone 10 mg oral 12h and 06h** No reaction: * Cycle 2: dexamethasone 6 mg oral 12h and 06h** * Cycle 3: dexamethasone 4 mg oral 12h and 06h** * Cycle 4 - …: dexamethasone 2 mg oral 12h and 06h**	H1 blocker po/ H2 blocker IV H1 blocker po/ H2 blocker IV	100	940	1	1%
Nokihara et al. 2016	Prospective	80-120 mg/m^2	* Cycle 1: dexamethasone 16 mg IV No reaction: * Cycle 2: dexamethasone 8 mg IV * Cycle 3: dexamethasone 4 mg IV * Cycle 4 - … : dexamethasone 2 mg IV	H1 blocker po/ H2 blocker IV	15	12 15 15 100	1/12 infusions 3/15 infusions 3/15 infusions 14/100 infusions	

**Dexamethasone oral 12h and 6h before initiation of the chemotherapy infusion; N: total number of patients who received chemotherapy; No. cycles: total number of chemotherapy cycles; No. patients: total number of patients with a hypersensitivity reaction; Percent patients: percentage of patients with a hypersensitivity reaction.

TABLE 2. Three-weekly paclitaxel.

Trial	Study design	Paclitaxel schedule	Premedication corticosteroids	Premedication H1 and H2 blockers	N	No. cycles	No. patients	Percent patients
O' Cathail et al. 2013	Prospective	175 mg/m^2	dexamethasone 20 mg oral 12h and 06 h** versus dexamethasone 20 mg IV	H1/ H2 blockers IV H1/ H2 blockers IV	93 55	238 147	5 8	5,4% *P= 0,07* 14,5%
Yanaranop et al. 2016	Prospective	175 mg/m^2	dexamethasone oral 12h and 06 h** versus dexamethasone 20 mg IV	H1/ H2 blockers IV	141 140		27 21	19,1% *P= 0,78* 17,9%
Tsavaris et al. 2005	Prospective	175-225 mg/m^2	dexamethasone 20 mg IV	H1/ H2 blockers IV	52		4	7,7%
Joly et al. 2011	Prospective	175 mg/m^2	dexamethasone 20 mg IV	H1/ H2 blockers IV	502		166	33,1% 2% SAE due to paclitaxel
Yamada et al. 2001	Prospective	210 mg/m^2	dexamethasone 20 mg IV	H1 blocker po/ H2 blocker IV	60	203	9	15%
Langer et al. 1995	Prospective	135-215 mg/m^2	dexamethasone 20 mg IV	H1/ H2 blockers IV	54	214	0	0%
Kosmas et al. 2006	Prospective	175-225 mg/m^2	dexamethasone 20 mg IV	H1/ H2 blockers IV	100		7	7,0%
Zidan et al. 2008	Prospective	175 mg/m^2	Cycle 1 - ... and no reaction: dexamethasone 20 mg oral 12h and 06 h**	H1 blocker po/ H2 blocker IV	80	464	3	4,0%
Sasada et al. 2007	Retrospective	175-200 mg/m^2	dexamethasone 20 mg oral 12 and 6h** versus dexamethasone 20 mg IV	H1 blocker po/ H2 blocker IV H1 blocker po/ H2 blocker IV	65 42		21 19	32,3% *P= 0,177* 45,2%
	Prospective	175 mg/m^2	dexamethasone oral 8 mg 12h before paclitaxel + dexamethasone 20 mg IV	H2 blocker IV H1 blocker (diphenhydramine + 437,5 mg calcium bromide IV)	22		14	63,6%

**Dexamethasone oral 12h and 6h before initiation of the chemotherapy infusion; N: total number of patients who received chemotherapy; No. cycles: total number of chemotherapy cycles; No. patients: total number of patients with a hypersensitivity reaction; Percent patients: percentage of patients with a hypersensitivity reaction; SAE: severe adverse event.

THREE-WEEKLY PACLITAXEL

A prospective study from O'Cathail et al. compared the reported HSR rates associated with IV and oral dexamethasone (*Table 2*). During three months the corticosteroids where administered orally (20 mg twelve and six hours before paclitaxel), the next three months they changed to IV dexamethasone (20 mg 30 minutes before paclitaxel) and then reverted again to oral corticosteroids for three months. HSR rates were 5,4% versus 14,5% for oral and IV dexamethasone, respectively.[15] Grade 3 HSR rates were 0% and 5,4%, respectively. O'Cathail also conducted a pooled analysis with data from two additional studies (Gennari et al. 1996 and Kwon et al. 2002) who also compared the oral and IV regimen, p=0,009 (*Table 4*).[15] A second prospective trial (Yanaranop et al.), double-blind and randomised, also compared the paclitaxel-associated HSR between oral and IV dexamethasone. There was no significant difference in overall (19,1% versus 17,9% respectively, p=0,78) and severe (0% versus 0,7%, p=0,498) HSR rate.[16] A third, but retrospective trial, Sasada et al., compared these two regimens. The overall inci-

dence, 32,3% (po) and 45,2% (IV), was not significantly different. However, the incidence of severe reactions, 1,5% and 14,3%, was significantly higher in the group with the IV corticosteroids premedication (p=0,027). They subsequently conducted a prospective trial with a modified premedication regimen (*Table 2*). A HSR was reported in 14 of the 22 enrolled patients (all grade ≤ 2).[17]

Kosmas and Tsavaris used a short-course premedication regimen, consisting of a single dose H1/H2 antagonists and IV dexamethasone 20 mg, 30 minutes prior to paclitaxel infusion.[18,19] HSR were recorded in 7,0% and 7,7%, respectively, all grade < 2 reactions.[18,19] Other prospective studies tried to prove that the same short-course corticosteroid premedication schedule is a safe alternative. In Yamada et al. grade 1 HSR were recorded in 9 out of 60 patients (15%).[20] Langer et al. reported no HSR.[21] The objective of Joly et al. was to analyse observed HSR from the randomised multicentre phase III CALYPSO trial. Data from 502 women with platinum-sensitive relapsed ovarian cancer, who were treated with 3-weekly paclitaxel and carboplatin, are available. An allergic reaction occurred in 33,1% of the patients (of which 8,8% were grade 3-4). Grade ≥ 2 reactions were attributed in 46/50 patients to carboplatin alone while 1/50 grade ≥ 2 reactions (2%) were due to paclitaxel infusion.[22]

Previously, we discussed the HSR rates when paclitaxel was given weekly in the prospective study from Zidan et al.[10] Zidan et al. prospectively treated 80 patients with paclitaxel, every three weeks. Oral dexamethasone 20 mg, twelve and six hours prior to paclitaxel, in combination with H1/H2 antagonists (30-60 minutes prior to paclitaxel) was given before the first cycle. If no reaction was seen during the first paclitaxel infusion this premedication regimen was continued. Three patients (4%) experienced a HSR, only during the first cycle. They concluded that it's safe to give premedication orally but they didn't give the short-course premedication regimen.[10]

DIFFERENT PACLITAXEL SCHEDULES (WEEKLY, TWO WEEKLY AND THREE WEEKLY)

In a multicentre study, Rosenberg et al. randomised patients between the standard oral corticosteroid regimen and IV short-course regimen. There were no statistically significant differences between the two groups, either overall (22,6% versus 24,2%) or for grade 3-4 (4,7% versus 5,1%) HSR (*Table 3*). There are no data about the differences between weekly and 3-weekly paclitaxel infusions.[23]

In Koppler et al. all patients received premedication with dexamethasone 40, 20 or 10 mg IV prior to the administration of paclitaxel. Only one patient experienced a grade 3 reaction after premedication with dexamethasone 10 mg, during the paclitaxel 100 mg/m^2 infusion.[24] The authors didn't report in this retrospective trial, whether grade 1 or 2 HSR were observed and there's no information about the paclitaxel infusion dose and the linked premedication dose.

Berger et al., prospectively reported the need of rescue medication after premedication with dexamethasone 20 mg IV immediately prior to paclitaxel and IV H1/H2 antagonists. The incidence of paclitaxel HSR during the first or second administration was 4%. When patients didn't experience a HSR after the first two administrations, no premedication was given for the subsequent infusions and no HSR occurred in these subsequent cycles.[25] After the publication of this study, the incidence of rescue medication was retrospectively characterised. After the first two cycles of paclitaxel-based chemotherapy, patients who didn't experience a HSR had their premedications discontinued. Two patients had a HSR (0,85%).[26]

In a single centre, retrospective study Yenilmez et al. compared the incidence of HSR in two different dexamethasone premedication regimens (*Table 3*).[27] They tried to stop all premedications or to lower the doses of dexamethasone after the first two infusions, if no reaction occurred. Rate of HSR were comparable: 7% and 5% respectively, p=0,7. All of the HSR occurred during the first paclitaxel infusion and were grade 2 or 3 reactions. No HSR occurred in the subsequent cycles, after stopping or lowering the premedications.[27]

NO DEFINED PACLITAXEL SCHEDULE

A retrospective trial from Markman et al. suggests that a short-course IV premedication regimen is as effective as the standard oral premedication regimen (*Table 4*). The incidence of HSR was 5% and 3%, respectively. This analysis is limited by its retrospective design and important information is missing (there are no data about the different HSR and the chemotherapy schedules).[28] In 1999, Markman et al. evaluated the HSR in more than 200 patients receiving a paclitaxel containing chemotherapy schedule. Nine percent experienced a HSR during the first cycle, after premedication with IV dexamethasone 20 mg, H1 and H2 antagonists.[29] Gennari et al. also compared the inci-

TABLE 3. Different paclitaxel schedules.

Trial	Study design	Paclitaxel schedule	Premedication corticosteroids	Premedication H1 and H2 blockers	N	No. cycles	No. patients	Percent patients
Koppler et al. 2001	Retrospective	135- 175 mg/m^2 q3w and 100 mg/m^2 q1w	dexamethasone 40 mg IV versus dexamethasone 20 mg IV versus dexamethasone 10 mg IV	H1/ H2 blockers IV H1/ H2 blockers IV H1/ H2 blockers IV	46 48 52	235 186 480	0 0 1	0% 0% 1,9%
Rosenberg et al. 2002	Prospective	67 mg/m^2 q1w and 200 mg/m^2 q3w	dexamethasone 20 mg oral 12h and 06 h** versus dexamethasone 20 mg IV	H1/ H2 blockers IV H1/ H2 blockers IV	106 99		24 24	22,6% 24,2%
Berger et al. 2012	Prospective	80-90 mg/m^2 q1w and 175 mg/m^2 q2w	* Cycle 1 + 2: dexamethasone 20 mg IV * No reaction, cycle 3- .. :. no premedication	* Cycle 1+2: H1/ H2 blockers IV * No reaction, cycle 3 - ... /	55	314	0	0%
Berger et al. 2015	Retrospective	80-90 mg/m^2 q1w and 175 mg/m^2 q2w or q3w	No reaction, cycle 3- ... : no premedication	No reaction, cycle 3- ... : /	234		2	0,85%
Yenilmez et al. 2016	Retrospective	1A. 60-80 mg/m^2 q1w 1B. 175 mg/m^2 q2w or q3w 2. 60-80 mg/m^2 q1w and 175 mg/m^2 q2w or q3w	1A. Cycle 1+2: dexamethasone 8 mg IV 1B. Cycle 1+2: dexamethasone 20 mg oral 12h and 06 h** 1A + 1B: No reaction, cycle 3- .. :. no premedication 2. Cycle 1+2: dexamethasone 10 mg IV 2. No reaction, cycle 3- ...: dexamethasone 8 mg IV	1A+ 1B. Cycle 1+2: H1/ H2 blockers IV 1A + 1B: No reaction, cycle 3 - ... : / 2. Cycle 1+2: H1/ H2 blockers IV 2. No reaction, Cycle 3- ...: /	24 36 60		4 0 0 3 0	16% 0% 0% 5% 0%

**Dexamethasone oral 12h and 6h before initiation of the chemotherapy infusion; N: total number of patients who received chemotherapy; No. cycles: total number of chemotherapy cycles; No. patients: total number of patients with a hypersensitivity reaction; Percent patients: percentage of patients with a hypersensitivity reaction; q3w: three weekly; q2w: two weekly; q1w: weekly.

dence of HSR after oral or IV dexamethasone prophylaxis. There was no significant difference between the two schedules.[30]

Two trials had a retrospective design with a short-course premedication regimen. In Micha et al. only 4 out of 183 patients (2,2%) experienced a HSR.[31] Bookman et al. reviewed the occurrence of HSR after the first two administrations of paclitaxel in 283 patients after premedication with IV dexamethasone 10 or 20 mg, diphenhydramine 50 mg and cimetidine 300 mg or ranitidine 50 mg administered 30 minutes prior to paclitaxel (dose and schedule unknown). All HSR were retrospectively recorded, based on written medical reports. HSR were recorded in 4,6%, with only two serious reactions (0,7%), during the first or second cycle. The subsequent cycles were not reviewed.[32]

In a small prospective trial (43 patients) by Parikh et al., a short-course premedication regimen was used. No HSR were recorded.[33]

A retrospective analysis by Kwon et al. suggests that the single-dose IV corticosteroid prophylactic regimen is associated with a higher rate of HSR than the two-dose oral regimen. One hundred and seven patients received the standard two-dose oral corticoste-

TABLE 4. No defined paclitaxel schedule.

Trial	Study design	Paclitaxel schedule	Premedication corticosteroids	Premedication H1 and H2 blockers	N	No. cycles	No. patients	Percent patients
Markman et al. 1997	Retrospective	Not defined	*Cycle 1: dexamethasone 20 mg oral 12h and 06 h** *Cycle 2 - ... : dexamethasone 20 mg IV	H1/ H2 blockers IV H1/ H2 blockers IV	157	1006		5% 1% (cycle 2: 3%)
Markman et al. 1999	Unclear	Not defined	dexamethasone 20 mg IV	H1/H2 blockers IV	200 +			9% cycle 1
Markman et al. 2000[36]	Retrospective	Not defined	dexamethasone 20 mg IV or oral dexamethasone 20 mg 12h and 06h**	H1/H2 blockers IV	450		44	9,8%
Parikh et al. 1996	Prospective	135 mg/m^2, 30-40 mg/m^2 CRT q1w	dexamethasone 16 mg IV	H1/H2 blockers IV	43	116	0	0%
Gennari et al. 1996	Unclear	135-225 mg/ m^2	prednisone 125 mg oral 12h and 06h** versus dexamethasone 20 mg IV	H1blocker IM/ H2 blocker IV H1blocker IM/ H2 blocker IV	90 47	469 151	7 3	7,7% *Not significant* 6,4%
Uziely et al. 1994	Unclear	135 mg/m^2	*Cycle 1: dexamethasone 20 mg oral 12h and 6h ** *Cycle 2 - ... : dexamethasone 12/8/4 mg oral 12 and 6h**	H1/H2 blockers IV H1/H2 blockers IV	68 22	 109	4 0	5,9% 0%
Micha et al. 1998	Retrospective	Not defined	dexamethasone 20 mg IV	H1/H2 blockers IV	183	1010	4	2,2%
Kwon et al. 2002	Retrospective	Not defined	dexamethasone 20 mg oral 12 and 6h** versus dexamethasone 20 mg IV	H1/H2 blockers IV H1/H2 blockers IV	107 110		8 19	7,5% *P= 0,04* 17,3%
Bookman et al. 1997	Retrospective	Not defined	dexamethasone 10 or 20 mg IV	H1/H2 blockers IV	283	534	13	4,6%

**Dexamethasone oral 12h and 6h before initiation of the chemotherapy infusion; N: total number of patients who received chemotherapy; No. cycles: total number of chemotherapy cycles; No. patients: total number of patients with a hypersensitivity reaction; Percent patients: percentage of patients with a hypersensitivity reaction; CRT: concurrent chemoradiotherapy; q1w: weekly.

roid regimen prior to 1998. After 1998, institution policy changed and 110 patients received IV short-course regimen. Seven and a half percent in the oral steroid group and 17,3% in the IV steroid group had a HSR. This difference was statistically significant (p=0,047). The difference in severe HSR was also significant, 0,9% versus 7,3%, respectively (p=0,026). The schedule and dose of paclitaxel isn't reported but their logistic regression analysis failed to reveal this as a significant factor. The two premedication regimens reflect treatment in different time periods.[34]

Uziely et al. tried to reduce the dose of corticosteroids with a tapering regimen (*Table 4*) to a minimum of 4 mg twelve and six hours prior to paclitaxel infusion. No HSR occurred in this small population of 22 patients.[35]

DISCUSSION

The initial development of paclitaxel as a cytotoxic drug was seriously hampered by the occurrence of severe HSR. The use of weekly paclitaxel chemotherapy is increasing but there are no published guidelines for HSR prophylaxis. Frequent use of corticosteroids are not only associated with increased adverse events.[8]

KEY MESSAGES FOR CLINICAL PRACTICE

1 Data from randomised trials on the optimal premedication regimen are lacking.

2 Tapering of dexamethasone is safe when paclitaxel is given weekly.

3 Three-weekly paclitaxel: HSR rates might be higher with a single-dose IV dexamethasone administration.

Glucocorticoids could selectively inhibit paclitaxel-induced apoptosis in human solid tumour cell lines in vitro and in an in vivo xenograft model, raising the question whether the pre-treatment with glucocorticoids might interfere with the therapeutic efficacy of paclitaxel.[37,38] In HER2-positive breast cancer patients paclitaxel is combined with trastuzumab. In vitro studies suggest that dexamethasone may also interfere with trastuzumab-induced cell growth inhibition.[39]
Dexamethasone reduces vascular permeability and maintains normal vascular responsiveness to circulating vasoconstrictor factors. They are given twelve and six hours prior to paclitaxel treatment because the onset of this anti-inflammatory action can be delayed (four to six hours).[40] When paclitaxel is given once every three weeks, O'Cathail conducted a prospective trial and reported an increase in severity and frequency of HSR when they changed the standard oral premedication regimen to the short-course IV dexamethasone regimen (p=0,07).[15] They also conducted a pooled analysis with data from two additional studies who directly compared the oral and IV regimen. The incidence of HSR rates compared by Gennari et al. were not significantly different but Kwon et al. concluded that the single-dose IV corticosteroid prophylactic regimen was associated with a higher rate of HSR (p=0,04).[30,34] In the pooled analysis the data from Sasada et al. weren't included: another (retrospective) trial which compared directly the HSR rates between the IV and oral regimen.[17] The incidence of severe reactions was significantly higher in the group with the IV corticosteroids premedication (p=0,027).[17] In the randomised prospective trial by Yanaranop et al. there was no significant difference between the two regimens.[16] Several prospective, single arm trials concluded that the short-course premedication regimen is a safe alternative.[18-22,33] But there was no direct comparison between the oral and IV regimens. Following this literature review, especially the data from the studies who directly compared the oral and IV regimens, a new paclitaxel premedication regimen was implemented in our institution. When paclitaxel once every three weeks is given, the standard oral dexamethasone regimen is used.
A literature review was done to see if the doses of steroid prophylaxes can be reduced in the weekly schedule. From early trials, it's known that the most HSR occur during the first or second paclitaxel doses and mostly within the first ten minutes of infusion.[41] Three prospective trials used a dexamethasone tapering regimen. Only in a minority of patients a grade 3 and 4 HSR occurred when the tapering regime begun.[9,10,12] In three small trials, if there was no HSR during the first or second paclitaxel infusion, no premedication was given: in the retrospective trials from Quock et al. and Yenilmez et al. and the prospective trial from Berger et al. No HSR occurred when the premedication was stopped.[13,25,27] Koppler et al. confirmed that reduced doses of IV dexamethasone resulted in low rates (0,3%) of serious HSR.[24] Most of these studies are small single centre trials and they use different paclitaxel doses, schedules and premedication regimens, therefore direct comparison isn't possible and a definitive recommendation still cannot be made. Based on these findings, it seems safe to lower the dexamethasone dose or to stop the premedication entirely when there's no HSR during the first or second paclitaxel infusion. Patients in our institution are therefore treated with oral dexamethasone 20 mg, given twelve and six hours prior to paclitaxel administration, in combination with H1/H2 antagonists. If no hypersensitivity reaction occurred during the first two cycles, IV H1 and H2 antagonists are given prior to paclitaxel infusion.

CONCLUSION

Despite the widespread use of weekly paclitaxel for many years, solid data on the optimal premedication schedule with a weekly paclitaxel regimen are lacking. It re-

mains important to be aware that a HSR can occur anytime when paclitaxel is infused. Emergency medication should be available to every patient receiving paclitaxel.

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