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Dexamethasone in the maintenance phase of acute lymphoblastic leukaemia treatment: Is the risk of lethal infections too high?

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ABSTRACT

We report an increased incidence of infectious deaths during maintenance treatment of the ninth protocol for acute lymphoblastic leukaemia of the Dutch Childhood Oncology Group (DCOG-ALL-9). The main difference in maintenance treatment between DCOG-ALL-9 and the DCOG-ALL-7 and DCOG-ALL-8 protocols is the interruption of methotrexate and 6-mercaptopurine by vincristine (2 mg/m^2 weekly) and dexamethasone (6 mg/m^2 daily) for 14 days every 7 weeks in the DCOG-ALL-9 protocol. The 1107 children treated with the DCOG-ALL-7, DCOG-ALL-8 or DCOG-ALL-9 protocol were included and screened for infectious death during maintenance treatment (July 1988–July 2002). Seven of the 510 children died of severe infections during the maintenance phase of DCOG-ALL-9, compared to none of the 597 patients during the DCOG-ALL-7 and DCOG-ALL-8 protocols (1.37% versus 0.0%; $p = 0.013$). Results from the current study suggest that repeated, prolonged exposure to dexamethasone results in an increase of lethal infections from 0% to 1.37%. In the dosing-schedule used, the advantage of dexamethasone may not outweigh the higher risk of infectious death.

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1. Introduction

A number of children with leukaemia die during treatment due to causes other than progressive leukaemia.[1] Since the start of the ninth protocol for acute lymphoblastic leukaemia treatment of the Dutch Childhood Oncology Group (DCOG-ALL-9), in January 1997, we have noticed an increase in lethal infections in children with acute lymphoblastic leukaemia (ALL). These patients presented with severe infections, mostly in the second half of the maintenance treatment. The main difference between the maintenance treatment of the DCOG-ALL-9 and the previous DCOG-ALL-7 and DCOG-ALL-8 protocols is the interruption of methotrexate (MTX) and 6-mercaptopurine (6MP) by vincristine (VCR) (2 mg/m^2 i.v. weekly) combined with dexamethasone (6 mg/m^2 p.o. daily) for 14 days every 7 weeks in the DCOG-ALL-9 protocol.

Dexamethasone has an important role in the treatment of ALL. The advantages of dexamethasone over prednisone in ALL treatment are its 5.5 to 16 times stronger antileukaemic activity[2,3] and its greater penetration into and the longer half-life in cerebrospinal fluid,[4] resulting in a decreased number of central nervous system relapses.[5,6] Randomised studies have shown that dexamethasone is appreciably more effective than prednisone in treatment of childhood ALL with significantly higher event-free survivals as a result.[7,8] However, dexamethasone also appears to have an anti-inflammatory action about nine times as strong as the anti-inflammatory action of prednisolone.[9]

In ALL induction therapy, an increased incidence in infectious deaths from 1% to 11% was reported when dexamethasone (6 mg/m^2/d) was substituted for prednisone (40 mg/m^2/d).[10] Others however, did not find an increase in infectious deaths, when dexamethasone (6 mg/m^2/d) was used instead of prednisone (40–60 mg/m^2/d) during ALL induction therapy.[7,11] During maintenance treatment in (standard risk) ALL, no difference was found in the incidence of infectious deaths between short courses (5 days every 4 weeks) of dexamethasone (6 mg/m^2/d) and prednisone (40 mg/m^2/d).[7] In contrast, the DCOG-ALL-9 protocol administered dexamethasone for 2 weeks every 7 weeks (in addition to two weekly VCR dosages), resulting in a higher dexamethasone dose-intensity and prolonged episodes of dexamethasone treatment. When scanning the literature, no reports of infectious deaths related to VCR use were found.

Patients treated for ALL often suffer from chemotherapy induced neutropenia, resulting in a diminished inflammatory response and an increased risk for serious infections. Therefore, standard treatment of febrile neutropenia consists of hospitalisation and empirical broad-spectrum intravenous antibiotic therapy.

In this article the patient and episode characteristics as well as the incidence of infectious deaths during the maintenance phase of the DCOG-ALL-9 treatment are described and compared with the incidence of infectious deaths during the maintenance treatment of the preceding DCOG-ALL-7 and DCOG-ALL-8 protocols.

2. Patients and methods

2.1. Patients

Of the 1289 children diagnosed in the Netherlands between July 1988 and July 2002 with ALL and treated with one of the consecutive DCOG-ALL-7, DCOG-ALL-8 or DCOG-ALL-9 protocol, 1139 (88%) entered maintenance treatment. The 1107 (97%) patients from whom we received complete data, concerning the start and stop dates of maintenance treatment, treatment outcome, and date of death when applicable, were included in this retrospective study. Data were complete in all DCOG-ALL-7 and DCOG-ALL-8 patients; 32 DCOG-ALL-9 patients were excluded due to missing data. Patient characteristics were obtained from the Dutch Childhood Oncology Group data office. Infectious death was defined as death with clinical and/or microbiologic evidence of a localised or generalised infection during complete remission. Death during maintenance was defined as death in the period from the day maintenance therapy started until the end of maintenance treatment. Neutropenia was defined as an absolute neutrophil count (ANC) $<0.5 \times 10^9$/l, or a leucocyte count $<1.0 \times 10^9$/l when ANC was not available.

2.2. Treatment

From July 1988 until January 1997, children with ALL were enrolled in DCOG-ALL-7[12] and DCOG-ALL-8 studies.[13] Briefly, maintenance treatment consisted of daily 6MP 50 mg/m^2 and weekly MTX 20 mg/m^2 orally. From January 1997 until January 2005, children with ALL were treated according to the DCOG-ALL-9 protocol. The induction therapy, central nervous system treatment and two intensification blocks (for high risk patients only) were followed by a maintenance phase up to 2 years after diagnosis. In contrast to the maintenance treatment of the two previous protocols, DCOG-ALL-9 consists of intrathecal triple medication every 7 weeks for 1 year, weekly doses of VCR 2 mg/m^2 intravenously two times and daily oral dexamethasone 6 mg/m^2 for 14 days, alternating with 5 weeks of weekly MTX 30 mg/m^2 (intravenously in high risk patients, orally in non-high risk patients) and daily oral 6MP 50 mg/m^2.

2.3. Statistical methods

The χ^2-test was used to compare infectious deaths during the maintenance treatment of the different ALL-protocols. The Cox proportional hazards model was used to test the influence of the duration of maintenance treatment on risk of infectious death. The Mann–Whitney *U* test was used to test whether there were age differences between the DCOG-ALL-7/8 and the DCOG-ALL-9 groups.

3. Results

During the DCOG-ALL-9 protocol, there were increasing reports of patients dying of infectious complications during their maintenance treatment. In the first 5.5 years, seven

infectious deaths occurred during the maintenance phase. Patient- and episode-characteristics are shown in Table 1. The patients (4 boys, 3 girls) had a median age of 5 years (range: 3–18 years), 3 were on high risk and 4 on non-high risk treatment. All but one patient had used dexamethasone recently, defined as within 2 days of presentation with infection. Five patients died in the second half of their maintenance phase. All but two patients had fever at admission, four in combination with neutropenia and/or leucocytopenia. At presentation most patients appeared in a relatively good clinical condition: five patients were alert; hypotension was reported in one patient (two unknown). Despite the prompt introduction of i.v. broad-spectrum antibiotic treatment, six patients deteriorated within 12 h after admission (one within 18 h). Causative pathogens were found in six patients. The incidence of infectious deaths during the maintenance therapy of DCOG-ALL-9 differed from the incidence of infectious deaths during the DCOG-ALL-7 and DCOG-ALL-8 protocols. DCOG-ALL-9 maintenance treatment was given to 510 evaluable patients. Seven of the 510 patients died of infectious complications. During the DCOG-ALL-7 and DCOG-ALL-8 protocols, 597 children started maintenance treatment and none of these children died of infectious complications or due to uncertain causes. There were significantly more infectious deaths during DCOG-ALL-9 than during the DCOG-ALL-7 and DCOG -ALL-8 maintenance treatments (7/510 versus 0/597; respectively, 1.37% versus 0.0%; $p = 0.013$), even more so when the uncertain causes of death ($n = 1$) were taken into account (8/510 versus 0/597; respectively, 1.57% versus 0.0%; $p = 0.007$). Additional adjustment for the duration of the maintenance treatment in the different protocols did not change these results. Therefore, the higher incidence of infectious deaths during the DCOG-ALL-9 protocol is not due to longer duration of the maintenance treatment of this protocol, compared to the previous protocols.

4. Discussion

Seven infectious deaths were seen during the first 5.5 years of DCOG-ALL-9 maintenance treatment, compared to none during DCOG-ALL-7 and DCOG-ALL-8 (1.37% versus 0.0%, respectively). These patients had hardly any clinical complaints and they presented relatively late with a severe infection. Five of the seven patients were still alert on admission, however, all but one patient's condition deteriorated quickly and despite intensive care treatment all seven patients died.

In this study 32 of the 542 patients who started DCOG-ALL-9 maintenance treatment had been excluded from analysis due to incomplete data. If these patients were included and analysed as having had no infectious deaths during maintenance treatment, they would decrease the incidence of infectious deaths from 1.37% to 1.29%. The difference in infectious deaths during DCOG-ALL-7 and DCOG-ALL-8 compared to DCOG-ALL-9 would still be significant ($p = 0.016$).

During the DCOG-ALL-6 maintenance treatment (1984–1988), which was identical to DCOG-ALL-9 maintenance treatment, the incidence of infectious deaths was even higher: 1.63% (3/184) (3-year event-free survival: 80%). However, the

Table 1 – Characteristics of seven patients with a lethal infection during the maintenance phase of their DCOG-ALL-9 treatment

	Patient						
	A	B	C	D	E	F	G
Age (years)	18	3	16	5	5	15	3
Sex	Female	Male	Male	Female	Male	Female	Male
Risk group	HR	NHR	HR	NHR	HR	NHR	NHR
Day – since start of last dexamethasone administration[a]	15	33	13	8	15	14	16
Period of dexamethasone use (HR 11, NHR 14 periods in total)	9th	12th	6th	12th	7th	7th	2nd
ANC at presentation (10^9/l)	NA	3.7	NA	0	0.1	2.9	0.03
ALC at presentation (10^9/l)	0.1	5.8	2.4	1.5	2.3	4.2	1.6
Mental state at presentation	Alert	Apathic and groggy	Alert	Somnolent	Alert	Alert	Alert
Hypotension at presentation	No	NA	NA	Yes	No	No	No
Febrile at presentation	Yes	No	No	Yes	Yes	Yes	Yes
CRP at presentation (mg/l)	238	5	1	83	74	469	111
Start of deterioration (hours after admission)	<2	<12	<18	3	∼4	∼10	∼10
Cultured microorganisms in blood (or otherwise mentioned)	*Escherichia coli*	*Shigella flexneri* 4a (faeces), *Toxoplasma myocarditis*	*Herpes simplex* virus	*Escherichia coli*	None	*Pseudomonas aeruginosa*, *Streptococcus mitis*	*Salmonella* (faeces)

HR: high risk; NHR: non-high risk; ANC: absolute neutrophil count; NA: not available; ALC: absolute leucocyte count; CRP: C-reactive protein; <: less than; ∼: about; ICU: intensive care unit.

a The first day of dexamethasone administration being day 1; day 14 being the last day of dexamethasone administration during that treatment cycle (7 weeks).

total number of patients was smaller.[14] In the UK ALL study, event-free survival was significantly improved among the 1603 randomised patients when dexamethasone was given instead of prednisone (84.2% versus 75.6% for the prednisone arm). Steroids were given 5 days out of every 4 weeks, total death in remission was, with 4.1% versus 3.0%, not statistically significantly different.[8] The study of the Children's Cancer Group of the United States[7] also used dexamethasone at a dose of 6 mg/m^2/d and showed a superior event-free survival than the prednisone arm of this randomised study; they reported one fatal complication among approximately 500 patients during maintenance. The more prolonged exposure to dexamethasone per treatment cycle, 14 consecutive days every 7 weeks (DCOG-ALL-9) versus 5 subsequent days every 4 weeks,[7] could explain the higher incidence of infectious deaths seen in the DCOG-ALL-9 group compared to Bostrom and colleagues (7/510 versus 1/about 500 patients, respectively).

A possible explanation for the increased incidence of infectious deaths under the DCOG-ALL-9 may lie in daily dexamethasone for 2 weeks in the maintenance treatment of the DCOG-ALL-9 protocol. In the literature, *in vitro* experiments are described in which effector cells of the innate immunity were (pre)incubated with dexamethasone, stimulated with several pro-inflammatory agents, and the pro-inflammatory cytokine production was measured. The inhibited production of inflammatory cytokines results in a slower rise of cytokine levels *in vitro*.[15–18] A longer preincubation with dexamethasone gave an even stronger inhibition of cytokine production *in vitro*.[17] *In vivo*, this attenuated cytokine response could have contributed to a diminished and later appearance of clinical symptoms of infection. This blunted inflammatory response will attenuate the clinical symptoms of a serious and potentially lethal infection. It can be hypothesised that the host response of these infectious deaths was diminished due to the use of dexamethasone.

Another explanation for the increased incidence of infectious deaths during the maintenance treatment of DCOG-ALL-9 may be an inadequate stress response. Stressors like inflammation stimulate the hypothalamic–pituitary–adrenal axis (HPA axis); this results in the increased synthesis and secretion of cortisol. Increased cortisol levels cause, e.g. anti-inflammatory effects and maintenance of the vascular tone. The HPA axis is of vital importance to build this stress response to an infection. Exposure to synthetic glucocorticosteroids can cause HPA axis suppression,[19–22] resulting in decreased cortisol levels in response to inflammatory stimuli. Several studies have shown great variation in the incidence and duration of HPA axis suppression.[23–25] A recent study in ALL patients demonstrated an attenuated cortisol response upon adrenocorticotropic hormone (ACTH) (low dose) in 46% of the patients 2 weeks after the discontinuation of 28 days prednisone.[26] Even after 1 week of prednisone treatment the ACTH-induced cortisol response is suppressed for at least 2 days after discontinuation.[27] We think that at the later phases of DCOG-ALL-9 maintenance treatment, that is after consecutive blocks of dexamethasone (14 days every 7 weeks), the HPA axis recovery might have become even worse, resulting in periods of (more severe) HPA axis suppression towards the end of the treatment. We hypothesise that this inadequate stress response results in a rapid deterioration of the patients' condition following a slow initiation of the inflammatory response.

5. Conclusion

Seven children died of infectious complications during the maintenance phase of the DCOG-ALL-9 protocol compared to none during the DCOG-ALL-7 and DCOG-ALL-8 protocols. The recurrent, prolonged use of dexamethasone could have been the crucial difference between DCOG-ALL-9 and DCOG-ALL-7/ 8. Dexamethasone treatment may result in a blunted inflammatory response with a slower and delayed rise of pro-inflammatory cytokine levels. This results in a delayed and masked presentation of infections in these patients. The effect of the recurrent and extended periods of dexamethasone usage may be accumulative and could lead to a hampered inflammatory response on the one hand and to an inadequate stress response on the other hand, resulting in an increased risk for lethal infections. Although dexamethasone has shown to have a stronger antileukaemic effect than prednisone[7,8] and could therefore be useful in a prolonged usage to maintain remission in ALL, the current findings suggest that this can lead to unacceptably high risks of lethal infections. It is questionable whether the advantage of dexamethasone administration in this repetitive and prolonged dosing-schedule during maintenance treatment, especially in the favourable prognostic groups, outweighs the disadvantage.

Conflict of interest statement

None declared.

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