[Original Research]

Are Corticosteroids Useful for End-stage Cancer Patients? A Retrospective Chart Review in the Palliative Care Unit

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Abstract: Corticosteroids are widely used to treat a variety of symptoms in terminal cancer patients. Although they have been shown to improve general fatigue, anorexia, nausea/vomiting, brain-metastasis-related symptoms, and dyspnea, further evidence is required. Major adverse effects due to corticosteroid administration include psychological symptoms, infections, muscular atrophy, osteoporosis, and peptic ulcers. Furthermore, symptoms that show as adverse events, such as the exacerbation of the primary disease, have also been observed. The timing of appearance and type of adverse effects remain to be clarified. In this study, we clarified the purpose, effectiveness, and adverse events of corticosteroid use in terminal cancer patients admitted to the palliative care unit. We conducted a chart survey involving 595 patients who were admitted to the Palliative Care Unit of Ashiya Municipal Hospital between July 1, 2012 and December 31, 2015. Corticosteroids were mainly used to relieve general fatigue and anorexia and were effective in over 70% of patients. Furthermore, there was a significant difference in the period of food intake between corticosteroid- and non-corticosteroid-treated patients with meals taken 3.9 and 6.8 days before death, respectively. The period from the start of administration until the appearance of adverse events was approximately 3 weeks. Delirium and oral candidiasis were the most frequent adverse events occurring in 26.5 and 13.8% of patients, respectively. Although there was no significant difference in incidence of delirium between patients receiving or not receiving corticosteroids, there was a significant difference in incidence of oral candidiasis. Corticosteroids may be safe and effective if the administration period is limited and used with a specific purpose.

Key words: adverse effect, palliative care, corticosteroid, cancer, end of lifecare, symptom management

INTRODUCTION

Corticosteroids are used as potent anti-inflammatory drugs to treat various diseases. Non-steroidal anti-inflammatory drugs (NSAIDs) exhibit anti-inflammatory effects through inhibitory actions on prostaglandin synthesis, whereas corticosteroids exhibit anti-inflammatory effects through various action mechanisms.[1)] Therefore, the efficacy of corticosteroids as anti-inflammatory drugs is higher than that of NSAIDs. However, adverse reactions related to long-term administration vary, and serious side effects have been reported. Therefore, adverse reactions in the initial phase of corticosteroid administration must also be considered.[2, 3)]

Terminal cancer patients have various symptoms, such as general fatigue, anorexia,[5–7)] nausea/vomiting,[8)] brain-metastasis-related symptoms,[9)] dyspnea,[10)] and carcinomatous lymphangiosis[11)] that are treated with corticosteroids[4)]. However, there is no clear evidence that corticosteroids are effective for these symptoms. In terminal cancer patients, it is unclear whether drug efficacy varies among individuals.

Major adverse effects of corticosteroid administration include psychological distress, infections, muscular atrophy, osteoporosis, and peptic ulcers.[12–14)] Symptoms that show as adverse events, such as the exacerbation of the primary disease, have also been observed. The timing of appearance and type of adverse reaction remain to be clarified. Furthermore, since some terminal cancer patients receive combination therapy, it may be difficult to assess the effects of corticosteroids alone due to interactions with other drugs.

In this study, we clarified the purpose, effectiveness, and adverse effects of corticosteroid use in terminal cancer patients admitted to the palliative care unit.

METHODS

We conducted a chart survey from the data of 595 patients admitted to the Palliative Care Unit of Ashiya Municipal Hospital between July 1, 2012 and December 31, 2015.

The survey items consisted of patient background, history of corticosteroid administration, and adverse events.

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In corticosteroid-treated patients, we clarified the type of administered corticosteroid, administration period, dose, purpose of administration, and administration route.

Corticosteroid effects on general fatigue, appetite loss, dyspnea, pain, and nausea were self-evaluated by the patients based on the following (extreme, 5; severe, 4; moderate, 3; weak, 2; or none, 0). Treatment by corticosteroids was considered effective if the patient showed improvement or had no symptoms in one or more stages.

For lower extremity edema, corticosteroid treatment that resulted in a reduction of 20% or more of the measurement site was considered effective.

Cancer lymphangiopathy, cerebral edema, interstitial pneumonia, and intestinal obstruction were diagnosed by X-ray and CT examination.

Hypercalcemia was considered to have improved when blood test results were within the normal range.

Tumor fever was considered to have improved when the body temperature was below 37℃.

Any food taken orally was considered a meal, and the number of days between the date of the last meal taken to the date of death was assessed. Patients who were not been able to intake food prior to corticosteroid use were excluded. Therefore, a total of 242 patients were assessed in this study. For statistical analysis, independence was tested using Student *t*-test. A *p*-value of 0.05 was considered significant.

Muscle weakness was assessed based on whether the patients were able to go to the bathroom independently. The number of days between the last date the patient was able to go to the bathroom independently to the date of death was assessed. Patients who were not able to walk prior to the administration of corticosteroids were excluded. Therefore, a total of 183 patients were assessed in this study. For statistical analysis, independence was tested using Student *t*-test. A *p*-value of 0.05 was considered significant.

Patients in whom the efficacy of corticosteroids could not be assessed, such as those who were discharged prior to being diagnosed with symptoms related to the side effects of corticosteroid use and those who died due to cancer, were defined as unknown.

For adverse events, the date when the symptom was first described in a chart was regarded as the date of appearance.

For statistical analysis, independence was tested using chi square test. A *p*-value of 0.05 was considered significant.

The corticosteroid conversion ratio based on prednisolone was as follows: betamethasone:prednisolone 0.75:5; dexamethasone:prednisolone 0.75:5; and hydrocortisone: prednisolone 20:5.

Patient background

The subjects consisted of 595 patients of whom 307 were males. Corticosteroids were administered to 427 (72%) patients. There was no difference in primary site or length of hospital stay between patients receiving or not receiving corticosteroids. However, the age group was older, and there was a gender difference (Table 1).

Table 1 Patient background

Corticosteroid	Treated	Non-treated	
Age (*SD*)	73 ± 12	80 ± 9	$p < 0.01$ *t*-test
Male	226	63	$p < 0.01$ Chi-squared test
Female	201	106	
Hospitalization (days ± *SD*)	32 ± 35	36 ± 53	$p = 0.25$ *t*-test
Primary tumor sites (*n*)			
Lung	104	32	NA
Bile duct, pancreas	66	21	
Colon, rectum	58	26	
Stomach	41	25	
Prostate, kidney, bladder	30	12	
Uterus, ovary	25	6	
Breast	29	5	
Liver	14	13	
Esophagus	18	4	
Blood, lymph	18	8	
Head and neck	3	9	
Sarcoma	3	0	
Other	19	8	

Double cancer, 3 patients.

RESULTS

Corticosteroids were effective in 64.9% of patients and ineffective in 15.0%. Their effects were unclear in 20.1%.

Regarding the route of administration, 59.5 and 46.8% of patients received intravenous and oral administration, respectively. There is duplication. Betamethasone, prednisolone, and dexamethasone were administered to 87.4, 7.7, and 3.0% of patients, respectively.

1. Purpose of administration and its effects

Of the various symptoms, 89% of corticosteroid administration was used to treat general fatigue and anorexia (Table 2). In addition, corticosteroids were used for a variety of symptoms that appeared at the end of life and were effective in over 70% of patients (Table 2).

Furthermore, the number of days without eating meals prior to death was significantly fewer in patients receiving corticosteroids (2.4 ± 3.1 days) compared with those not receiving corticosteroids (6.8 ± 18.4 days) (Fig. 1).

The number of days that the patient was able to walk independently was 4.9 ± 5.7 days prior to corticosteroid administration and 14.6 ± 20.4 days before non-administration, and there was a significant difference between those receiving and not receiving corticosteroids (Fig. 2).

2. Adverse events during the survey period

Delirium was the most frequent adverse event and was observed in 26.5% of patients followed by oral candidiasis (13.8%). Other adverse events included insomnia and hot flushes (Table 3), which appeared 3 weeks after the start of administration.

There was no significant difference in the incidence of delirium between those receiving or not receiving corticosteroid administration (Fig. 3). However, there was a significant difference in the incidence of oral candidiasis between corticosteroid- and non-corticosteroid-treated patients (Fig. 4) with the former having a twofold higher incidence.

DISCUSSION

First, in the Palliative Care Unit, corticosteroids were used to relieve various symptoms, such as general malaise and anorexia, and the response rate exceeded 70%. Furthermore, the corticosteroid-treated group was able to intake food longer than the non-corticosteroid-

Table 2 Purpose of administration and its effects

Symptom	pts	Dose (mg ± *SD*)	Administration (days ± *SD*)	Improvement (%)
Fatigue	261	17.5 ± 11.1	11.0 ± 14.3	73.6
Anorexia	117	15.8 ± 10.0	16.1 ± 18.7	76.9
Dyspnea	36	27.5 ± 26.1	12.5 ± 20.1	55.6
Edema	35	25.9 ± 11.1	7.4 ± 6.3	77.1
Ileus	25	42.6 ± 11.1	3.3 ± 1.9	76.0
Pain	18	26.5 ± 18.7	2.0 ± 0.8	72.2
Nausea/Vomiting	17	12.6 ± 6.2	14.6 ± 17.5	70.6
Edema in the brain	17	28.4 ± 19.3	4.4 ± 3.7	80.0
Lymphangiosis carcinomatosis	14	37.8 ± 10.0	2.8 ± 1.1	92.9
Peritonitis carcinomatosis	7	25.6 ± 15.6	4.7 ± 4.7	57.1
Tumor fever	6	36.4 ± 44.7	6.8 ± 6.7	80.0
Interstitial pneumonia	3	18.2 ± 11.4	8.7 ± 11.6	100.0
Hypercalcemia	3	40.0 ± 13.3	4.3 ± 3.1	100.0

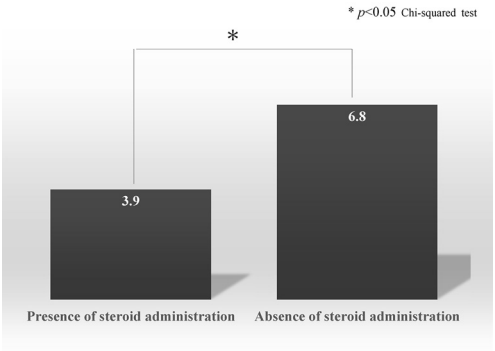

Fig. 1 Interval during which it was possible to take meals before death

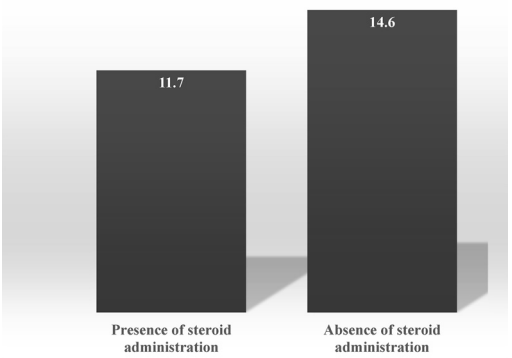

Fig. 2 Interval during which walking was possible before death

Table 3 Adverse events and time of onset

	Patient (*n*)	%	Mean (days)	Median (days)
Delirium	113	26.5	21.0	10.0
Oral candidiasis	57	13.8	22.8	20.0
Insomnia	28	6.6	6.1	3.0
Hot flushes	6	1.4	22.3	9.5
Infection	25	5.9	24.1	13.0
Moon face	7	1.6	18.7	15.0

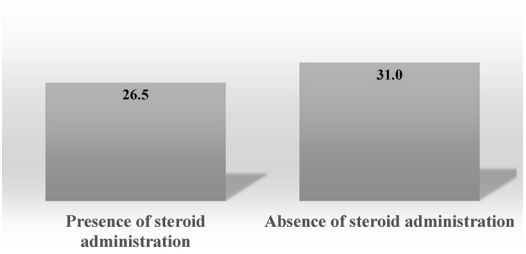

Fig. 3 Relationship between the appearance of delirium and steroid administration

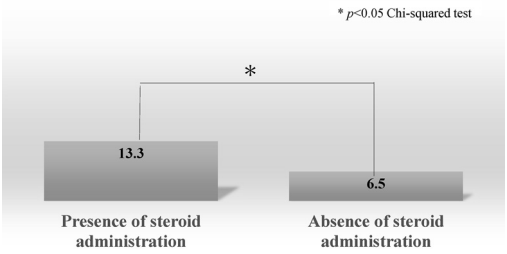

Fig. 4 Relationship between oral candidiasis and steroid administration

treated group prior to death. In addition, those treated with corticosteroids were able to walk independently 10 days longer. These results show that corticosteroids may lower the risk of flail development in patients with terminal cancer. However, the effect of corticosteroids on preventing muscle weakness is unclear, and our study methods may have affected psychological effects such as general fatigue and depression.

Second, terminal-stage delirium occurs in many patients. Results for the occurrence of delirium in medical in-patients were available for 42 cohorts. Prevalence of delirium at admission ranged from 10 to 31%, incidence of new delirium per admission ranged from 3 to 29% and occurrence rate per admission varied between 11 and 42%[15]. On the other hand, among 73 eligible patients, complete data were available from 61 on admission and 49 after 2 weeks. Twenty-six patients (43%) met delirium criteria on admission.[16] However, the effect of corticosteroids on delirium remains to be clarified. We showed that there was no difference in the incidence of delirium between corticosteroid- and non-corticosteroid-treated patients. Furthermore, the mean interval from the start of corticosteroid administration until the appearance of delirium was 21 days with a median of 10 days. Therefore, there may be no causal relationship in most patients. These results may also suggest that it is not necessary to avoid the use of corticosteroids, considering the appearance of delirium, although we cannot conclude that corticosteroids are safe with respect to delirium. These results indicate that corticosteroids are not safe for delirium, but there is no need to refrain from using them due to the onset of delirium, and careful administration may be expected to improve QOL.

Lastly, this study showed that the incidence of oral candidiasis significantly increased when the corticosteroid administration period exceeded 3 weeks. As for side effects, only oral candida was significant, so it is considered that the QOL of terminally ill patients will be improved by the effect of corticosteroids by actively performing oral care.

Furthermore, systemic infectious diseases were also observed; however, their incidences were low. Therefore, when administering corticosteroids over a long period, the risk of infections must be considered.

CONCLUSIONS

Corticosteroids may be safe and effective if the administration period is limited and used with a specific purpose.

Limitations. This study was a retrospective single-center study. Adverse events included those that could not be definitively evaluated as adverse reactions.

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