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Alteration in the Frequency, Severity and Duration of Chemotherapy-induced Mucositis in Hamsters by Interleukin-11

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Ninety-five young, male Golden Syrian hamsters were randomly divided into five equally sized groups. One group served as a placebo control while the animals in the others received one of four doses of interleukin-eleven (IL-11) twice daily given by subcutaneous injection beginning on the first day of chemotherapy (day 0) and continuing to day 14. Mucositis was induced with 5-fluorouracil using a standard regimen of 60 mg/kg, intraperitoneally on days 0 and 2 followed by superficial mucosal irritation on day 4. Animals were evaluated daily beginning on day 6. Mucositis was assessed using a standardised technique in which randomly numbered daily mucosal photographs were scored by three blinded independent observers at the conclusion of the experiment. IL-11 favourably affected the frequency, severity and duration of mucositis. This phenomenon appeared to be dose dependent. Hamsters receiving 30 and 100 μg per day of IL-11 demonstrated significantly ($P<0.05$) lower mucositis scores than did either the control or animals receiving 3 or 10 μg per day, although the latter had marginal beneficial effects. Additionally, survival was significantly better for hamsters receiving higher doses of IL-11 (85%) compared to the placebo control (46%). IL-11 administration also favourably affected weight loss. While stimulation of platelet production was noted in animals receiving IL-11, a lack of difference in bone marrow cellularity between test and control animals suggests that the mechanism by which IL-11 modifies mucositis is mediated at the epithelial or connective tissue level rather than through the marrow. The kinetics of IL-11 alteration of mucositis induction supports such a hypothesis. Further investigation is currently underway to establish a definitive mechanism by which IL-11 protects the oral mucosa.

Keywords: mucositis, interleukin-11, chemotherapy, animal model, hamster

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INTRODUCTION

LIKE THE rest of the gastrointestinal tract, the mouth is often affected by nonspecific, direct toxicity as a consequence of cancer chemotherapy [1, 2]. The condition which develops, ulcerative mucositis, is a common and severe side effect of antineoplastic therapy [3]. An overall frequency of approximately 40% has been reported to be associated with the use of a variety of agents including 5-fluorouracil, cytarabine (ara/c) and etoposide and methotrexate [4–8]. There are approximately 1 000 000 episodes of the condition yearly in the United States. As other types of complications are more easily controlled, the importance of oral mucositis as a dose-limiting toxicity is increasing [9, 10]. In addition to severe pain, mucositis results in the destruction of the oral mucosa as an anatomic barrier. Hence, the mouth becomes a portal of entry for enteric bacterial, fungal and viral organisms. The development of chemotherapy-induced myelosuppression follows soon after mucositis, resulting in the mouth becoming a frequently identifiable source of sepsis in the granulocytopenic cancer patient [11, 12].

Current therapy for mucositis is largely palliative. Secondary infections are treated with appropriate antimicrobial medication. Unfortunately, there is no therapy which adequately prevents or reduces the frequency, severity or course of chemotherapy-induced mucositis.

Active biologic manipulation of the epithelium and marrow may hold a key to improving the oral changes in response to chemotherapy. Anecdotal data suggest that cytokine mediated stimulation of bone marrow may favourably affect the course

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of mucositis [13]. Timed modification of the renewal rate of the basal oral epithelium might also be beneficial [14].

Interleukin-11 (IL-11) is a 199-amino acid polypeptide which was first described by Paul *et al.* [15]. IL-11 is produced *in vivo* by stromal cells in marrow and, as recently reported, by other connective tissue cells [16]. IL-11 is unique among other cytokines for its lack of disulphide bonds and its isoelectric point of 11.7 being highly basic. A relatively wide range of *in vitro* and *in vivo* activities have been associated with the cytokine [17]. Among those of particular relevance to patients receiving cancer chemotherapy are stimulation of megakaryocytopoiesis, stimulation of platelet and neutrophil recovery after chemotherapy-induced myelosuppression and production of increased acute phase protein levels. Based on these activities, we reasoned that the administration of IL-11 might favourably impact the course and duration of ulcerative mucositis induced by 5-fluorouracil (5-FU) in an animal model.

MATERIALS AND METHODS

This study was performed in two parts. Since there was no data to demonstrate IL-11 activity in hamsters, a preliminary investigation was conducted to show IL-11 action and to determine optimum dose relative to the stimulation of platelet production in these animals. We then investigated the effect of IL-11 administration on the frequency, severity and duration of ulcerative mucositis induced by 5-FU.

Recombinant human IL-11 (Genetics Institute, Cambridge, Massachusetts, U.S.A.) purified from *Escherichia coli*, was used [18].

Experiments were conducted in accordance with guidelines set by the Harvard Medical Area Standing Committee on Animals.

Animals

Male Golden Syrian hamsters obtained from Charles River Laboratories, aged 5–7 weeks, were used. Animals were caged in small groups and fed standard hamster chow and water *ad libitum*.

Preliminary dose ranging study

The initial phase of this investigation consisted of a dose ranging study to determine an efficacious dose of IL-11 in the hamster. Sixty animals were randomly divided into five equally sized groups. Hamsters were injected with IL-11, twice daily, subcutaneously, for 5 days. Three animals from each group were sacrificed on days 3, 5, 6 and 8 and automated platelet counts were obtained. The following groups were studied: group 1, placebo; group 2, 10 μg/day; group 3, 30 μg/day; group 4, 100 μg/day; group 5, 300 μg/day.

Animals were sacrificed on day 8.

Efficacy study

Ninety-five hamsters were divided into five equally sized groups. Animals were dosed twice daily (9 am and 4 pm) on days 0–14. 5-Fluorouracil (60 mg/kg) was administered intraperitoneally on days 0 and 2. The cheek pouch mucosa was superficially irritated on day 4. This technique has been repeatedly demonstrated to produce ulcerative mucositis which mimics the human condition [14, 19, 20]. Beginning on day 6 and continuing throughout the remainder of the experiment (day 16), daily photographs, using a standardised technique, were obtained of the left buccal pouch. On days 8, 12 and 16, three animals from each group were randomly selected for sacrifice. Biopsies were obtained of the oral mucosa and bone marrow. The right femur was dissected and placed in Zenker's solution for decalcification, prior to histologic evaluation to evaluate bone marrow cellularity. The percentage of cellularity was determined in a blinded fashion by evaluation of a minimum of five fields (low power) per specimen. Peripheral blood was obtained from the same animals to determine white blood cell and platelet counts.

The following groups were studied: group 1, vehicle control (autologous hamster serum and PBS); group 2, IL-11 3 μg/day; group 3, IL-11 10 μg/day; group 4, IL-11 30 μg/day; group 5, IL-11 100 μg/day.

Each dilution of IL-11 was prepared in 0.5 ml of sterile PBS containing 0.5% autologous hamster serum. IL-11 was received in a concentration of 5 mg/ml; 2 vials of 25 mg in 5 ml were stored at 4°C after being diluted to 0.2 mg/ml. The stock solution was diluted on the day of use.

At the conclusion of the experiment, all film was developed and the photographs were randomly numbered. Each photograph was then graded, in blinded fashion, on a standardised 10 point severity scale (10 being the highest). For descriptive purposes, scores of 2–4 are considered to represent slight mucositis, 4–6 are considered to represent moderate mucositis, and >6 severe mucositis. Statistical significance between groups was determined using Student's *t*-test.

RESULTS

Twice daily, subcutaneous injections of IL-11 for 5 consecutive days resulted in stimulation of platelet production (Table 1). The response appeared to be dose-dependent to the extent that the rate and magnitude of platelet stimulation were

Table 1. Results of preliminary dosing study in which hamsters were treated twice daily with subcutaneous injections of IL-11 for 5 days. Automated platelet counts (K/μl) performed on samples taken from three animals in each group on days 3, 5, 6 and 8, demonstrated a dose-related stimulation by IL-11 of platelet production

Day	Group 1 (Control)	Group 2 (10 μg)	Group 3 (30 μg)	Group 4 (100 μg)	Group 5 (300 μg)
3	610.7±70.2	296	506.5±31.5	917±50.6	954±32.7
5	702.7±48.8	932±296.3	1235±39.8	1348±85.7	1436±26.7
6	555.7±67.4	1293±64.5	1439±116.2	1530.3±62.3	1576.3±160.8
8	594.3±81.4	904.7±93.4	1039±151.1	1002±139.2	1095±22.5

greatest in hamsters receiving daily doses of 100 or 300 μg compared to animals receiving 10 or 30 μg. However, significant platelet stimulation was noted in all groups compared to the placebo control on days 5, 6 and 8. Peak platelet number was observed in all groups on day 6, which was one day following the last dosing of IL-11.

The development, severity and frequency of chemotherapy-induced mucositis was markedly reduced in animals treated with twice daily, subcutaneous injections of IL-11. Additionally, changes in weight and survival were favourably affected by the administration of IL-11.

Animals receiving placebo developed moderate to severe mucositis by day 9 (Figs 1, 2). The mean mucositis score for the placebo group was 6.8 on day 10. Slight improvement of mucositis scores was noted in response to low doses of IL-11; little difference was noted between scores in animals receiving either 3 or 10 μg of IL-11. Mean mucositis scores in these groups on day 10 were 5.6 and 5.5, respectively. In contrast, administration of higher doses (30 and 100 μg) of IL-11 had a profound and favourable effect on the development of mucositis (Fig. 3). Day 10 mucositis scores in both groups were markedly less than the control or low dose IL-11 groups. Hamsters receiving 30 μg daily demonstrated a day 10 score of 3.8 and animals injected with 100 μg were similar with a mean day 10 score of 3.6. Importantly, this trend was noticeable as early as day 6 of the experiment; IL-11 prevented the development of significant mucositis in both high dose groups.

To evaluate clinical significance, the percentage of animals in each group with at least moderate mucositis was evaluated (Fig. 4). Significant differences were noted between animals receiving placebo or low dose IL-11 and those receiving high dose IL-11. For example, whereas almost 80% of animals in the placebo group had mucositis scores equal to or greater than

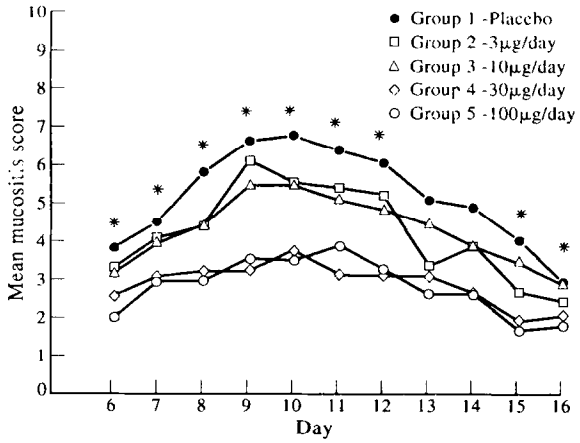

Fig. 1. Effect of twice daily, subcutaneous injections of IL-11 on the development of mucositis induced by 5-FU. Daily photographs of each cheek pouch, randomly numbered at the completion of the experiment, were graded in blinded fashion by three observers. Statistically significant differences between the placebo controls and animals treated with 30 or 100 μg/day of IL-11 are indicated by *.

Fig. 2. Clinical appearance of cheek pouch in representative hamster from placebo group on day 9. Mucositis score = 8.

Fig. 3. Clinical appearance of cheek pouch in representative hamster receiving 100 μg of IL-11 daily (group 5) on day 9. Mucositis score = 1.

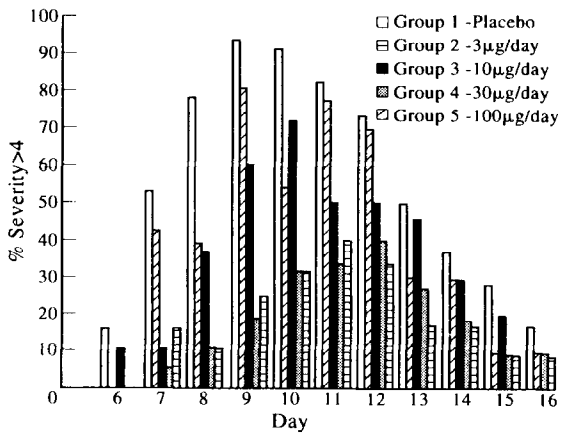

Fig. 4. Percentage of animals in each group with at least moderate mucositis by day. Moderate mucositis was defined as a score of >4 on a 10 point scale.

5 on day 8, only 10% of animals which received either 30 μg or 100 μg of IL-11 had scores of this magnitude. This trend was noted throughout the course of the study.

Both survival and weight changes were favourably affected by the administration of the higher doses of IL-11. Whereas significant mortality among animals of the placebo group was noted during the course of the experiment (Fig. 5), survival among animals receiving IL-11 was significantly better ($P < 0.05$). While survival also appeared to be related to dose, this trend was less dramatic than noted with mucositis.

Absolute daily weights and changes in weight were evaluated for each group (Fig. 6). All animals demonstrated a decrease in weight of about 10–20% between days 6 and 11. However, this change was less in animals receiving the higher doses of IL-11 than the placebo controls or animals treated with lower doses of IL-11.

Three animals from each group were randomly selected for sacrifice on days 8, 12 and 16. Peripheral blood was obtained and automated white blood cell counts and platelet counts were performed. Platelet numbers were elevated in all groups receiving IL-11, except for the 30 μg group on day 8 (Table 2). A peak in platelet counts was noted on day 12 for all groups, including the placebo control. No differences were noted in white blood cells (WBC) between the placebo control and 3 μg group at any of the time periods studied (Table 3). In contrast,

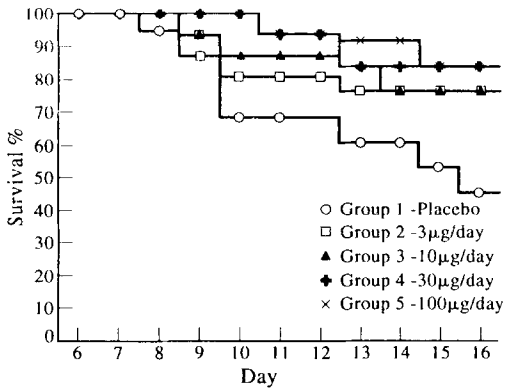

Fig. 5. Comparison of survival among treated animals and the placebo control. Note that the three animals in each group intentionally sacrificed on days 8, 12 and 16 for histologic and peripheral blood studies, are excluded from this comparison.

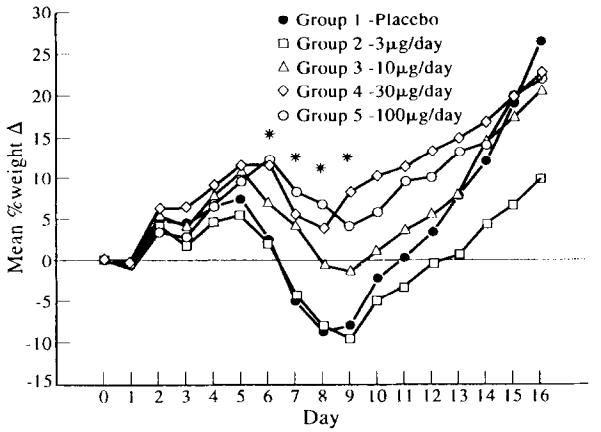

Fig. 6. Differences in weight among experimental groups. Statistical significance ($P > 0.05$) is indicated by *.

animals in the other groups demonstrated higher WBC than the control on day 12. Only animals receiving 10 μg had an increased WBC on day 8. By day 16, all WBC converged, although the WBC of hamsters receiving the higher two doses of IL-11 were higher than the control.

Following preparation in Zenker's solution, cross sections of femurs were evaluated for bone marrow cellularity (Table 4). Increased cellularity was noted on day 8 in hamsters receiving 100 μg of IL-11 compared to the other groups. On day 12, no significant differences were noted among groups. This trend persisted on day 16; no significant differences in cellularity could be appreciated between samples obtained from hamsters in all groups except the 30 μg group, in which cellularity was slightly higher.

Histologic changes in oral mucosal tissue were evaluated in three randomly selected animals from each group on days 8, 12 and 16. Biopsies of left cheek pouch mucosa were fixed in formalin, sectioned and stained with haematoxylin and eosin. Specimens were read blindly and the degree of inflammatory infiltrate was scored on a three point scale (0 = no inflammation). To ensure consistency, a second observer read selected specimens. No significant differences in grading were noted when the scores from each observer were compared.

There did not appear to be a relationship between the degree of inflammatory infiltrate, the dose of IL-11 administered or the extent of mucositis. Animals receiving placebo demonstrated a linear increase in mucosal inflammation from day 8 to day 16 that was bracketed in severity by animals receiving both high and low doses of IL-11.

DISCUSSION

Ulcerative mucositis has become increasingly important as a dose-limiting toxicity for cancer chemotherapy. It appears that lesions are initially the consequence of the cytotoxic and cytostatic effects of the drug on the basal cells of the oral epithelium (direct stomatotoxicity) [21]. Subsequently, local secondary infection, precipitated by the patient's myelosuppressive state, results in prolongation and exacerbation of areas of ulceration (indirect stomatotoxicity) and often predisposes to sepsis. Given the rate of epithelial renewal, direct stomatotoxicity generally begins within 5 days of the administration of drug. In contrast, indirect stomatotoxicity corresponds to the development of myelosuppression and is usually not a factor until 10 days following treatment [22].

Sensitivity of the oral mucosa to direct stomatotoxicity is markedly affected by the rate of epithelial proliferation. As a result, children are more likely to develop mucositis than are adults [23]. Cytokine stimulation of epithelium with epidermal growth factor increases the frequency and severity of mucositis [20]. In contrast, successful reduction in the intensity of mucositis has been achieved with the topical application of TGF-β3 prior to the administration of 5-fluorouracil in an animal model [14].

The effects of cytokine stimulation of marrow on the severity, course and duration of ulcerative mucositis is unclear. Whereas some anecdotal observations in patients receiving GCSF suggest a favourable impact of the protein on mucositis [13], other observers have not found such an effect [24]. Similarly, the effects of GM-CSF on mucositis are equally inconclusive.

IL-11 has a variety of *in vivo* and *in vitro* activities. Among those of potential importance to the present investigations are

Table 2. Platelet counts (K/μl) of samples taken from three animals in each treated and control group on days 8, 12 and 16

Day	Group 1 (Control)	Group 2 (3 μg)	Group 3 (10 μg)	Group 4 (30 μg)	Group 5 (100 μg)
8	462.3±113.7	980±284.7	833±365.6	541.3±255.4	1451.3±198.2
12	2117.3±163	6161±593.2	2656±615.7	2667.7±169.6	2789±162.8
16	460.6±63.7	1284.6±453.1	912.4±250.6	1129.4±256.8	1210.4±370.5

Table 3. White blood counts (K/μl) of samples taken from three animals in each treated and control group on days 8, 12 and 16

Day	Group 1 (Control)	Group 2 (3 μg)	Group 3 (10 μg)	Group 4 (30 μg)	Group 5 (100 μg)
8	17±2.8	18.7±2.7	29.8±21	11.7±9.9	21.6±0.3
12	14.6±2.8	15.1±2.0	30.2±9.2	29±4.8	36.6±2.3
16	7.5±0.8	7.5±2.1	8.4±2.7	10.3±1.5	14.2±2.8

Table 4. Comparison of percentage of bone marrow cellularity among treated and control animals. Bone marrow biopsies were obtained from three animals from each group on days 8, 12 and 16 and evaluated in a blinded fashion

Day	Group 1 (Placebo)	Group 2 (3 μg/day)	Group 3 (10 μg/day)	Group 4 (30 μg/day)	Group 5 (100 μg/day)
8	53.3	61.7	58.3	38.3	71.7
12	76.7	75.0	68.3	70.0	80.0
16	73.3	83.3	78.3	90.0	73.3

those related to platelet stimulation and neutrophil recovery following myelosuppressive therapy [25]. Based on the reported marrow activities of IL-11, we reasoned that administration of IL-11 to hamsters might favourably shorten the course of mucositis. We did not anticipate that IL-11 would impact on the development, frequency or severity of direct stomatotoxicity.

In contrast to our expectations, twice daily, subcutaneous administration of IL-11 resulted in a marked reduction in the development of mucositis, the number of days of moderate or severe mucositis and the overall frequency and severity of mucositis. In addition, animals receiving IL-11 demonstrated less weight loss and better survival than did the placebo controls. This effect appeared to be related to the dose of IL-11 administered and was apparent within 4 days following 5-FU administration.

That IL-11 produced marrow stimulation in the hamster was successfully demonstrated in our initial experiment in which significant, dose-related platelet stimulation was observed. In spite of this finding, it seems likely that the effect of IL-11 on mucositis and its consequent morbidity and mortality was a local effect on the epithelium, rather than mediated through the marrow. The evidence for this hypothesis is largely circumstantial. Whereas the maximum platelet stimulation was not seen in treated animals until day 12, suppression of mucositis was noted in animals receiving 30 μg/day or 100 μg/day by day 7. Weight loss, which probably reflects the hamster's inability to tolerate food and overall systemic condition, was already significantly more pronounced in the control and low dose (3 μg/day) groups by day 6. Additionally, while significant clinical differences in mucositis were noted by day 6, differences in bone marrow cellularity among groups were not apparent. Neither was there an apparent relationship between the degree of oral mucosal inflammatory infiltration, IL-11 administration and degree of mucositis. Finally, earlier animal studies suggest that IL-11 stimulates recovery of intestinal mucosal injury produced by cytoablative drugs and radiation [26].

While it is likely that the cytoprotective effects of IL-11 are mediated locally, the mechanism of action is presumably different than that hypothesized for TGF-β3 [14]. Comparison of the curves for mucositis development between the two cytokines demonstrates that the transient interruption in epithelial proliferation induced by TGF-β3 resulted in improved mucositis scores after a short lag time. In contrast, the protective effects of IL-11 were immediate.

IL-11 is clearly a pleiotropic cytokine which may have a role in the prevention of ulcerative mucositis induced by cancer chemotherapy. While it is likely that this effect is not mediated through the myeloproliferative actions of IL-11, the mechanism by which the cytokine protects the oral mucosa is currently unknown. Additional studies are being undertaken to define the mechanism by which IL-11 exerts this effect.

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