POSSIBLE ROLE OF GRANULOCYTE COLONY-STIMULATING FACTOR (FILGRASTIM) IN THE MANAGEMENT OF RADIATION INDUCED ORAL MUCOSITIS AND DYSPHAGIA

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PURPOSE

In a pilot study among head and neck cancer patients (mainly oral cavity and oropharynx carcinomas), we tested the possible role of granulocyte colony-stimulating factor (Filgrastim) in the management of acute side-effects of radiotherapy (mucositis and dysphagia).

RATIONALE (1)

Oral mucositis and dysphagia are common acute consequences of radiotherapy for cancers in the head and neck area.

They may compromise the tumour control by limiting the dose and /or unduly protracting the treatment.

Severe side-effects occur especially in case of accelerated hyperfractionation and / or concomitant chemotherapy.

RATIONALE (2)

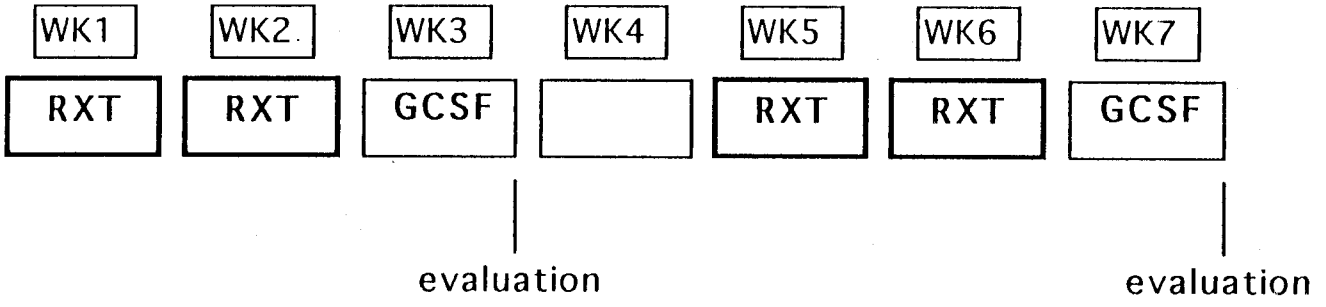
Granulocyte colony-stimulating factors used to reverse chemotherapy induced neutropenia have been shown to unexpectedly improve the level and the severity of associated mucositis. A similar effect was observed in bone marrow transplant patients and also on mucosal reactions occurring during non myelotoxic chemotherapy.

PATIENTS

	Study group	Control group
cases	21	68
males/females	15/6	48/20
age mean	63	61
range	32-95	41-94
oropharynx	12	34
oral cavity	8	23
nasopharynx	1	4
other sites	0	7
exclusive RT	10	36
post-operative RT	11	32
Filgrastim	21	0
conventional support	21	68

METHODS (1)

RADIOTHERAPY



gamma rays of cobalt - portals as usual practice
4 weeks of treatment splitted by a 15 days rest
48 Gy (minimum tumour dose) in 12 fractions
BED = 67 Gy_{10} and 112 Gy_3 (or TDF 103)

GRANULOCYTE STIMULATING FACTOR

Filgrastim 3 microgm/kg/day subcutaneously
at the end of each radiotherapy sequence
for 6 consecutive days

METHODS (2)

ASSESSMENT OF MUCOSAL SIDE-EFFECTS

- after each radiotherapy sequence
- on the last day of GCSF administration

A. MUCOSITIS grade 0 to 5

grade 0 no reaction
grade 1 mucosal congestion - intense redness (enanthema)
grade 2 dotted mucositis - rare sparse fibrinous patches
grade 3 patchy fibrinous exudate
grade 4 confluence of fibrinous lesions over the whole mucosa
grade 5 ulceration - hemorrhage - necrosis

B. DYSPHAGIA grade 0 to 5

grade 0 no complaints
grade 1 little discomfort in swallowing but eats as usual
grade 2 mild dysphagia, food cut into small pieces or pureed
grade 3 solid diet too painful but liquids well accepted
grade 4 marked difficulties in swallowing liquid meals
grade 5 tube feeding mandatory

C. SCORE OF INTOLERANCE C = sum of A + B

minor < 3
intermediate 3 - 5
major > 5

RESULTS (1)

AT MID-TREATMENT

% MUCOSITIS

Grade	Filgrastim group	Control group
1	7	11
2	53	24
3	40	60
4	0	5

% DYSPHAGIA

Grade	Filgrastim group	Control group
1	13	15
2	56	40
3	31	38
4	0	7

Trend towards positive effect of Filgrastim treatment but statistical significance at the 0.05 level not reached if Yates correction for small samples is taken into account.

RESULTS (2)

AT THE END OF TREATMENT

% MUCOSITIS

Grade	Filgrastim group	Control group
1	33	4
2	34	21
3	33	68
4	0	7

p < 0.01
(X2 = 11.75 for 3 degrees of freedom, including Yates correction)

% DYSPHAGIA

Grade	Filgrastim group	Control group
1	29	8
2	57	41
3	14	44
4	0	7

p < 0.06
(X2 = 7.22 for 3 degrees of freedom including Yates correction)

RESULTS (3)

AT MID-TREATMENT

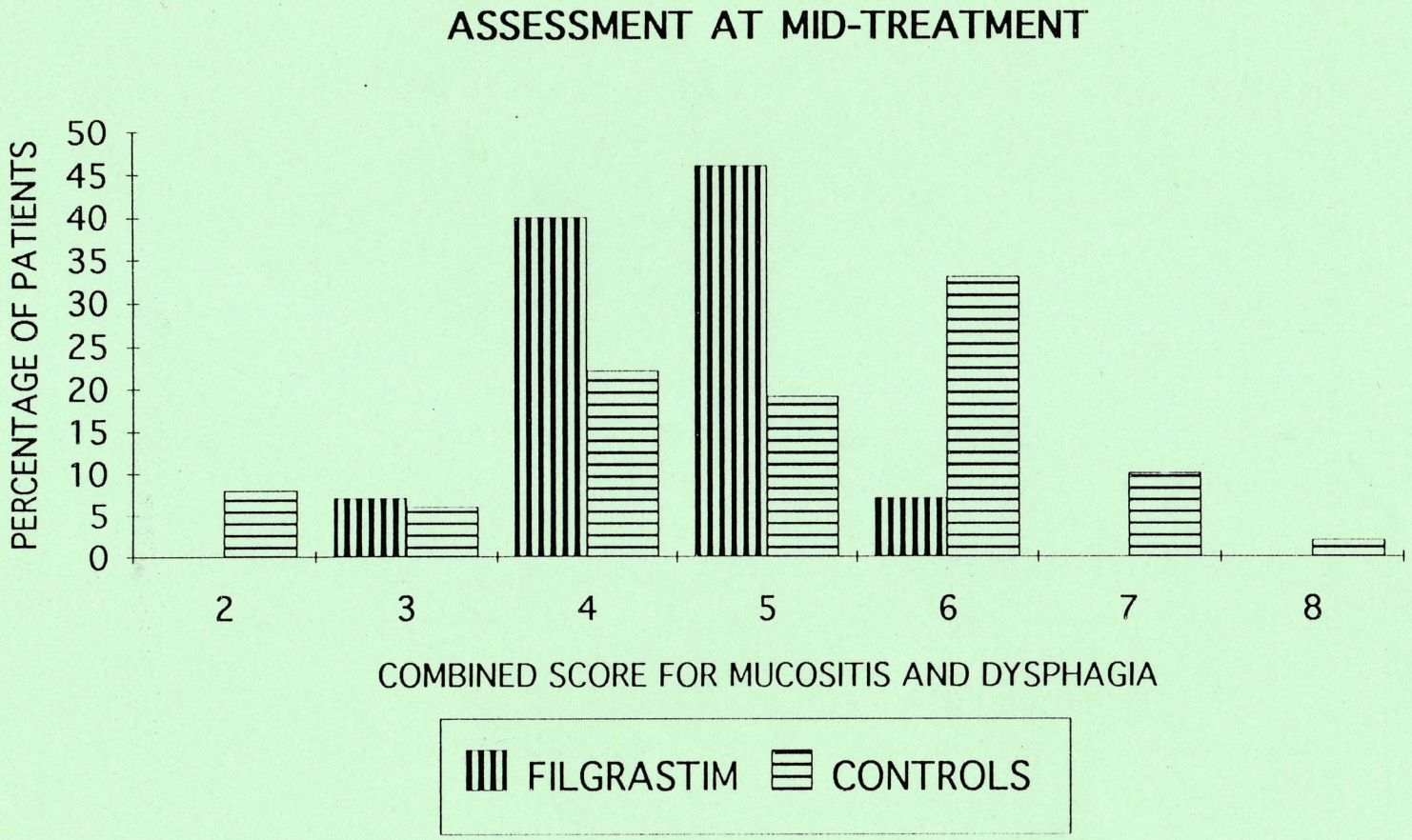
Score of intolerance (%)	Filgrastim group	Control group
minor	0	8
intermediate	93	47
major	7	45

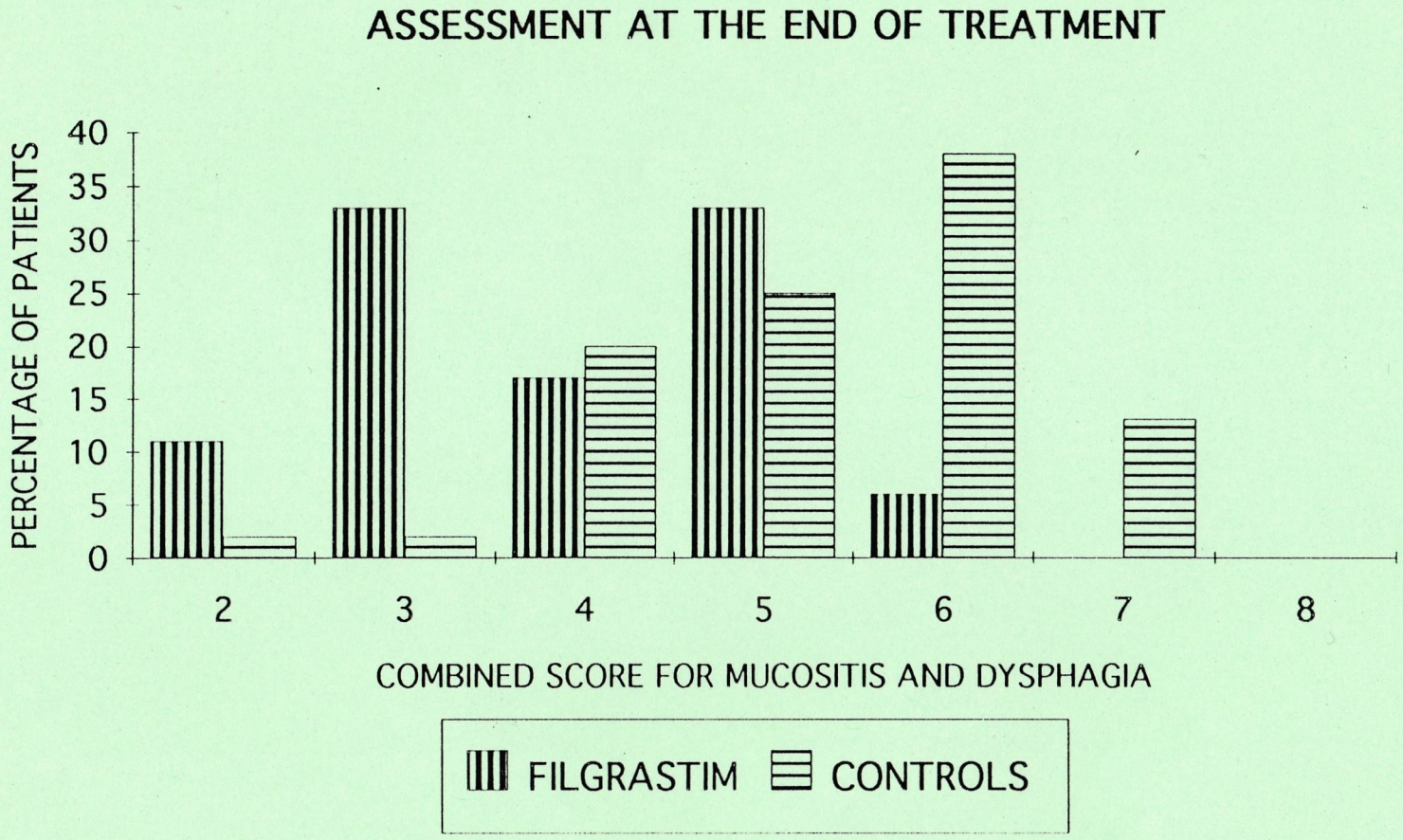
$p < 0.05$
(X2 = 7.68 for 2 degrees of freedom, including Yates correction)

AT THE END OF TREATMENT

Score of intolerance (%)	Filgrastim group	Control group
minor	11	2
intermediate	83	47
major	6	51

$p < 0.01$
(X2 = 9.49 for 2 degrees of freedom, including Yates correction)


ASSESSMENT AT MID-TREATMENT
PERCENTAGE OF PATIENTS
50
45
40
35
30
25
20
15
10
5
0
2
3
4
5
6
7
8
COMBINED SCORE FOR MUCOSITIS AND DYSPHAGIA
FILGRASTIM
CONTROLS


ASSESSMENT AT THE END OF TREATMENT
PERCENTAGE OF PATIENTS
40
35
30
25
20
15
10
5
0
2
3
4
5
6
7
8
COMBINED SCORE FOR MUCOSITIS AND DYSPHAGIA
FILGRASTIM
CONTROLS

SUMMARY AND CONCLUSIONS

Radiotherapy for head and neck cancers is usually associated with oro-pharyngeal mucositis resulting in some degree of dysphagia. In case of accelerated hyperfractionation or concomitant chemotherapy, these acute complications may constitute a limiting factor for an optimal tumour control. Among 21 patients (mainly oral cavity and oropharynx cancers) we tested the possible role of granulocyte colony-stimulating factor in the management of mucosal side-effects. Filgrastim (3mcg/kg/day) was injected for 6 days at the end of each sequence of a split-course irradiation given at full dose exclusively or post-operatively. Correlations were made with a group of 68 patients comparable for tumour site and radiotherapy but receiving conventional support only.Evaluation of objective and functional reactions as well as combined scoring of oral and pharyngeal intolerance favor the hypothesis of a possible positive effect of Filgrastim treatment. These results have to be parallelled with already known effects of GCSFand GMCSF on chemotherapy induced mucositis. Owing to the benefit suggested by this pilot study it seems worth while determining proper administration in terms of dosing and timing.Strictly comparative trials will afterwards eventually bring the necessary statistical ascertainment.