APPENDIX 10: RANDOMIZED CONTROLLED TRIALS OF KERATINOCYTE GROWTH FACTOR FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – OUTCOMES

First Author (Year)	**COMPARISONS**	**OUTCOMES**				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Blijilevens (2013) [1]	KGF (pre-post) versus placebo	224	57	No significant difference in maximum severity of oral mucositis between placebo and KGF given either pre-/post HSCT (OR 0.7, 95% CI 0.4 to 1.3) or pre-HSCT (OR 1.2, 95% CI 0.6 to 2.4)	Area under curve for MTS not significantly different between placebo and pre-/post HSCT or pre-HSCT	17/224 adverse events leading to KGF discontinuation vs 1/57 with placebo. 1 fatal adverse event with KGF vs 0 with placebo
Jagasia (2012) [2]	KGF (pre-post) versus placebo	77	78	Incidence of grade 3-4 oral mucositis (73% placebo vs 81% KGF) similar between groups	Not reported	Study drug-related adverse events 23 (32%) placebo vs 31 (40%) KGF. Most commonly reported treatment-related adverse events: skin/subcutaneous such as rash, pruritus and erythema
Le (2011) [3]	KGF versus placebo	94	94	Incidence of severe oral mucositis significantly lower for KGF than placebo (54% vs 69%; P=0.041)	Average MTS scores in KGF vs. placebo arms (mean 1.7 vs 1.9) (NS)	Adverse events similar between arms (98% KGF, 93%, placebo). Most common study drug–related adverse events rash, flushing and dysgeusia
Henke (2011) [4]	KGF versus placebo	92	94	Incidence of severe oral mucositis significantly lower for KGF than placebo (51% vs 67%; P=0.027)	No difference in MTS between groups	Adverse events with difference in incidence of at least 5% between KGF and placebo arms: dysphagia (35% and 21%), dehydration (6% and 14%), leukopenia (13% and 21%), insomnia (5% and 13%), fatigue (8% and 15%), diarrhea (12% and 5%), mucosal inflammation (4% and 11%), asthenia (14% and 8%), headache (10% and 4%), abdominal pain (8% and 2%), and back pain (6% and 1%)
Vadhan Raj (2010) [5]	KGF versus placebo	32	16	KGF reduced cumulative incidence of grade 2 or higher WHO mucositis (44% vs 88%; P<0.001) and grade 3 or 4 mucositis (13% vs 51%; P=0.002)	Mouth pain scores significantly lower with KGF (1 vs 5; P=0.002)	Main adverse effects thickening of oral mucosa (72% KGF vs 31% placebo; P=0.007) and altered taste
Brizel (2008) [6]	KGF versus placebo	67	32	Median duration grade 2 or higher mucositis non-significantly shorter for KGF than placebo (6.5 vs 8.1 weeks; P=0.157)	Not reported	Type, incidence, and severity of adverse events similar between treatment groups
Rosen (2006) [7]	KGF versus placebo	28	36	During first chemotherapy cycle, incidence of WHO grade 2 or higher mucositis lower with KGF than with placebo (29% vs 61%; P=0.016)	Cycle 1, MTS scores significantly lower with KGF (P=0.005)	Oral-related adverse events more frequent in KGF vs placebo. During cycle 1, 50% KGF patients oral-related adverse event vs 33% placebo (P=0.13)

First Author (Year)	COMPARISONS	OUTCOMES				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Blazar (2006) [8]	KGF versus placebo	69	31	Difference in mean severity of oral mucositis significantly lower with KGF than with placebo (2.8 vs 2.3; P=0.01)	Not reported	Most adverse events similar frequencies in two groups. Skin reactions significantly more common with KGF (94% vs 68%; P<0.01)
Freytes (2004) [9]	KGF versus placebo	28	14	Grade 2 to 4 mucositis 100% for placebo, 64% for 25 mcg/kg (P=0.041 vs placebo), and 50% for 50 mcg/kg (P=0.006 vs placebo). Worst OMAS scores 14.0, 14.1, and 9.6 respectively for placebo, 25 mcg/kg and 50 mcg/kg groups (NS)	Mean worst pain on swallowing score 4.6, 4.8, and 2.1 for the placebo, 25 mcg/kg, and 50 mcg/kg groups, respectively. Difference between 50 mcg/kg and placebo significant (P=0.044)	Adverse events similar for KGF and placebo groups
Spielberger (2004) [10](companion paper: [11])	KGF versus placebo	106	106	Incidence of WHO grade 3 or 4 mucositis 63% with KGF and 98% with placebo (P<0.001). Median duration of mucositis 3 days (range 0 to 22) with KGF vs 9 days (range 0 to 27) with placebo (P<0.001)	KGF associated with significant reduction in MTS (P<0.001)	Adverse events more often with KGF: skin and oral epithelium effects such as rash, pruritus, erythema, paresthesia, mouth and tongue disorders, and taste alteration
Meropol (2003) [12]	KGF versus placebo	54	27	Frequency grade 2 to 4 mucositis 43% with KGF compared with 67% with placebo (P=0.06)	Area under the curve for mouth soreness: Placebo (mean 35.9; SE 7.6) vs. KGF (mean 30.3; SE 4.8)	Skin and oral events occurred in 13 of 18 patients treated with 60 and 80 mcg/kg of KGF and three of 11 patients treated with 40 mcg/kg

Abbreviations: KGF – keratinocyte growth factor; HSCT – hematopoietic stem cell transplantation; OR – odds ratio; CI – confidence interval; MTS – Mouth and Throat Soreness; WHO – World Health Organization; OMAS – Oral Mucositis Assessment Scale; NS – not significant

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