

Bölüm

7

ORAL VE GASTROİNTESTİNAL MUKOZİT YÖNETİMİ

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GİRİŞ

Mukozit, mukoza ülseri veya iltihabıdır. İmmün yetmezlik durumlarında ortaya çıkabilen ve malign hastalıkların tedavisinde doz azaltıcı ya da tedaviyi kesici sonuçlara yol açabilen önemli bir toksitedir. Mukozit hafif bir inflamasyondan derin ülsere kadar değişen düzeylerde ve ağızdan anüse kadar tüm gastrointestinal sistem mukoza­sında patolojik değişikliklere yol açabilen bir süreçtir(1).

Mukozit patobiyolojisi; eşlik eden hastalıklar, enfeksiyonlar, uzun süreli steroid kullanımı, kullanılan ilaçların her bireyin metabolizmasına göre farklı etkinlik göstermesi gibi hasta ile ilişkili faktörler ve hastanın kullanmakta olduğu ilaçlara göre değişebilir.

Mukozitin evresine göre; ülserasyonlar, disfaji, odinofaji, gastrit, ishal, malabsorpsiyon, enfeksiyon ve kanama gibi farklı klinik yansımaları olabilir. Hastanede yatan hastalarda hastane kalis süresinde ve tedavi maliyetlerinde artışa neden olabilir (2).

Mukozitin etkin tedavi yöntemleri kısıtlı olduğu için; kanıt dayalı rehberlerin, hem mukozit oluşmasını engellemek için hem de tanı ve tedavi süreçlerinde kullanımını oldukça önemlidir. Günümüzde hastaların tedavisini planlarken, mukozit riskini belirleyen bir rehber oluşturulmamıştır. Fakat moleküler yöntemlerin gelişmesi ve farmakogenomiklerin kullanımına girmesi ile mukozit

oluşma riski öngörelebilir hale getirilebilir (2,3). Bu şekilde, meydana gelebilecek olası komplikasyonları en aza indirgeyecek bireyselleştirilmiş tedaviler planlanabilir.

MUKOZİT PATOLOJİSİ

Mukozal bariyerde oluşan hasarın ortaya çıkma aşamaları şu sırayla olmaktadır (4,5) :

- Başlangıç Aşaması: Kemoterapi ve radyoterapi, doğrudan ve serbest oksijen radikalleri aracılığıyla DNA'ya zarar verir.
- Upregülasyon ve haberci sinyallerinin üretilmesi: Fibroblastlar, makrofajlar, endotel ve epitel hücreleri tarafından nükleer faktör kappa beta (NFκ-B) gibi transkripsiyon faktörlerinin aktivasyonu ve sonrasında tümör nekroz faktör alfa (TNF-α), interlökin-1 (IL-1), interlökin-6 (IL-6) gibi proinflamatuar sitokinler dahil protein salınımı olur.
- Sinalizasyon ve amplifikasyon: Proinflamatuar sitokinler biriktikçe, çevre dokulara doğrudan zarar vermeye başlarlar. Bu aşama klinik olarak mukozit gelişiminden hemen öncedir.
- Ülserasyon ve iltihap: Mukozal bütünlüğün bozulması sonucunda klinik olarak ağrılı lezyonlar ortaya çıkar ve bakteriler ülser yüzeyine kolonize olarak mukozal harabiyeti daha da arttırlar. Eğer hastada nötropeni varsa, bu durum bakteriyemi ve sepsis gelişimine neden olabilir.

¹

ğini karşılayabilecek beslenme şekli ve beslenme yolunun oluşturulması çok önemlidir.

Sonuç olarak; bu hastalarda yeterli farkındalıkın oluşturulması, oluşabilecek ciddi ve ölümçül komplikasyonların önüne geçilmesi, erken tanınması ve nihayetinde önlenmesine yönelik çalışmalar yapılması açısından önem taşımaktadır.

KAYNAKLAR

1. Duncan M, Grant G. Review article: oral and intestinal mucositis - causes and possible treatments. *Aliment Pharmacol Ther* 18: 853-874, 2003.
2. Niscola P, Romani C, Cupelli L. Mucositis in patients with hematologic malignancies: an overview. *Haematologica* 92: 222-231, 2007.
3. Mitchell EP. Gastrointestinal toxicity of chemotherapeutic agents. *Semin Oncol* 33: 106-120, 2006.
4. Slieker RC, Relton CL, Gaunt TR, et al. Age-related DNA methylation changes are tissue-specific with ELOVL2 promoter methylation as exception. *Epigenetics Chromatin* 2018; 11:25.
5. vB Hjelmborg J, Iachine I, Skytthe A, et al. Genetic influence on human lifespan and longevity. *Hum Genet* 2006; 119:312.
6. Lalla RV, Peterson DE. Treatment of mucositis, including new medications. *Cancer J* 12: 348-354, 2006.
7. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab* 1996; 81:2468.
8. Hofman MA, Swaab DF. Living by the clock: the circadian pacemaker in older people. *Ageing Res Rev* 2006; 5:33.
9. Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. *JAMA* 1992; 267:1806.
10. Cowdry EV. Problems of ageing: biological and medical aspects, 2nd ed, Williams & Wilkins, Baltimore 1942.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13:818.
12. Galetta F, Franzoni F, Femia FR, et al. Lifelong physical training prevents the age-related impairment of heart rate variability and exercise capacity in elderly people. *J Sports Med Phys Fitness* 2005; 45:217.
13. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100:1619.
14. Shlush LI. Age-related clonal hematopoiesis. *Blood* 2018; 131:496.
15. Buscarlet M, Provost S, Zada YF, et al. DNMT3A and TET2 dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. *Blood* 2017; 130:753.
16. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014; 371:2488.
17. Pinto A, De Filippi R, Frigeri F, et al. Aging and the hemopoietic system. *Crit Rev Oncol Hematol* 2003; 48:S3.
18. P, Romani C, Cupelli L, Scaramucci L, Tendas A, Dentamaro T, Amadori S, de Fabritiis P. Mucositis in patients with hematologic malignancies: an overview. *Haematologica* 2007; 92:222-231.
19. Fuentes E, Palomo I. Role of oxidative stress on platelet hyperreactivity during aging. *Life Sci* 2016; 148:17.
20. Franchini M. Hemostasis and aging. *Crit Rev Oncol Hematol* 2006; 60:144.
21. Isaia G, Greppi F, Ausiello L, et al. D-dimer plasma concentrations in an older hospitalized population. *J Am Geriatr Soc* 2011; 59:2385.
22. Duncan M, Grant G. Review article: oral and intestinal mucositis - causes and possible treatments. *Aliment Pharmacol Ther* 2003; 18: 853-874.
23. Bagnara GP, Bonsi L, Strippoli P, et al. Hemopoiesis in healthy old people and centenarians: well-maintained responsiveness of CD34+ cells to hemopoietic growth factors and remodeling of cytokine network. *J Gerontol A Biol Sci Med Sci* 2000; 55:B61.
24. Solomon R, Cherny NI. Constipation and Diarrhea in Patients with Cancer. *Cancer J*. 2006; 12: 355-364.
25. Davilla ML. Neutropenic enterocolitis. *Curr Opin Gastroenterol* 22:44-47.
26. Stringer AM, Gibson RJ, Bowen JM, Logan RM, Yeoh AS-J, Kefe DMK. Chemotherapy-Induced Mucositis: The Role of Gastrointestinal Microflora and Mucins in the Luminal Environment. *J Support Oncol* 2007;5:259-267
27. Wisinski K, Benson AB. Chemotherapy-Induced Mucositis: Focusing on Diarrhea. *J Support Oncol* 2007;5:270-271.
28. NCI CTCAE (2018). (Erişim 28 Mart 2018 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8_5x11pdf)
29. Yamamoto K, Takeshita K, Shimokawa T, et al. Plasminogen activator inhibitor-1 is a major stress-regulated gene: implications for stress-induced thrombosis in aged individuals. *Proc Natl Acad Sci U S A* 2002; 99:890.
30. Hall KE, Proctor DD, Fisher L, Rose S. American gastroenterological association future trends committee report: effects of aging of the population on gastroenterology practice, education, and research. *Gastroenterology* 2005; 129:1305.
31. Dunn-Walters DK, Howard WA, Bible JM. The Aeging Gut. *Mech Ageing Dev* 2004; 125:851.
32. Smith CH, Boland B, Daureeawoo Y, et al. Effect of aging on stimulated salivary flow in adults. *J Am Geriatr Soc* 2013; 61:805.
33. Leehan KM, Pezant NP, Rasmussen A, et al. Fatty infiltration of the minor salivary glands is a selective feature of aging but not Sjögren's syndrome. *Autoimmunity* 2017; 50:451.
34. Nagler RM, Hershkovich O. Age-related changes in unstimulated salivary function and composition and its relations to medications and oral sensorial complaints. *Aging Clin Exp Res* 2005; 17:358.
35. Dua KS, Surapaneni SN, Kurabayashi S, et al. Effect of aging on hypopharyngeal safe volume and the aerodigestive reflexes protecting the airways. *Laryngoscope* 2014; 124:1862.

36. Mei L, Dua A, Kern M, et al. Older Age Reduces Upper Esophageal Sphincter and Esophageal Body Responses to Simulated Slow and Ultraslow Reflux Events and Post-Reflux Residue. *Gastroenterology* 2018; 155:760.
37. Lasch H, Castell DO, Castell JA. Evidence for diminished visceral pain with aging: studies using graded intraesophageal balloon distension. *Am J Physiol* 1997; 272:G1.
38. Kekki M, Samloff IM, Ihamäki T, et al. Age- and sex-related behaviour of gastric acid secretion at the population level. *Scand J Gastroenterol* 1982; 17:737.
39. Feldman M, Cryer B, McArthur KE, et al. Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. *Gastroenterology* 1996; 110:1043.
40. Salles N. Basic mechanisms of the aging gastrointestinal tract. *Dig Dis* 2007; 25:112.
41. Drozdowski L, Thomson AB. Aging and the intestine. *World J Gastroenterol* 2006; 12:7578.
42. Veldhuis JD. Altered pulsatile and coordinate secretion of pituitary hormones in aging: evidence of feedback disruption. *Aging (Milano)* 1997; 9:19.
43. Parlesak A, Klein B, Schecher K, et al. Prevalence of small bowel bacterial overgrowth and its association with nutrition intake in nonhospitalized older adults. *J Am Geriatr Soc* 2003; 51:768.
44. Man AL, Bertelli E, Rentini S, et al. Age-associated modifications of intestinal permeability and innate immunity in human small intestine. *Clin Sci (Lond)* 2015; 129:515.
45. Hilton D, Iman N, Burke GJ, et al. Absence of abdominal pain in older persons with endoscopic ulcers: a prospective study. *Am J Gastroenterol* 2001; 96:380.
46. Wade PR, Hornby PJ. Age-related neurodegenerative changes and how they affect the gut. *Sci Aging Knowledge Environ* 2005; 2005:pe8.
47. Lagier E, Delvaux M, Vellas B, et al. Influence of age on rectal tone and sensitivity to distension in healthy subjects. *Neurogastroenterol Motil* 1999; 11:101.
48. Cowen T, Johnson RJ, Souheyre V, Santer RM. Restricted diet rescues rat enteric motor neurones from age related cell death. *Gut* 2000; 47:653.
49. Lyon C, Clark DC. Diagnosis of acute abdominal pain in older patients. *Am Fam Physician* 2006; 74:1537.
50. Gundling F, Seidl H, Scalercio N, et al. Influence of gender and age on anorectal function: normal values from anorectal manometry in a large caucasian population. *Digestion* 2010; 81:207.
51. Bitar KN, Patil SB. Aging and gastrointestinal smooth muscle. *Mech Ageing Dev* 2004; 125:907.
52. Commane DM, Arasaradnam RP, Mills S, et al. Diet, ageing and genetic factors in the pathogenesis of diverticular disease. *World J Gastroenterol* 2009; 15:2479.
53. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. *Pharmacol Rev* 2004; 56:163.
54. Schmucker DL. Aging and the liver: an update. *J Gerontol A Biol Sci Med Sci* 1998; 53:B315.
55. Wachsmuth M, Hbner A, Li M, et al. Age-Related and Heteroplasmoy-Related Variation in Human mtDNA Copy Number. *PLoS Genet* 2016; 12:e1005939.
56. Tietz NW, Shuey DF, Wekstein DR. Laboratory values in fit aging individuals--sexagenarians through centenarians. *Clin Chem* 1992; 38:1167.
57. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997; 61:331.
58. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol* 2003; 38:843.
59. Froom P, Miron E, Barak M. Oral anticoagulants in the elderly. *Br J Haematol* 2003; 120:526.
60. Valdivieso V, Palma R, Wünckhaus R, et al. Effect of aging on biliary lipid composition and bile acid metabolism in normal Chilean women. *Gastroenterology* 1978; 74:871.
61. Watanabe Y, Kuboki S, Shimizu H, et al. A New Proposal of Criteria for the Future Remnant Liver Volume in Older Patients Undergoing Major Hepatectomy for Biliary Tract Cancer. *Ann Surg* 2018; 267:338.
62. Yang W, Xie Y, Song B, et al. Effects of aging and menopause on pancreatic fat fraction in healthy women population: A strobe-compliant article. *Medicine (Baltimore)* 2019; 98:e14451.
63. Denic A, Lieske JC, Chakkera HA, et al. The Substantial Loss of Nephrons in Healthy Human Kidneys with Aging. *J Am Soc Nephrol* 2017; 28:313.
64. Denic A, Mathew J, Lerman LO, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med* 2017; 376:2349.
65. Ungar A, Cristofari C, Torrini M, et al. Changes in renal autacoids in aged human hypertensives. *J Physiol Pharmacol* 2000; 51:619.
66. Field TS, Gurwitz JH, Glynn RJ, et al. The renal effects of nonsteroidal anti-inflammatory drugs in older people: findings from the Established Populations for Epidemiologic Studies of the Elderly. *J Am Geriatr Soc* 1999; 47:507.
67. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med* 1999; 106:13S.
68. Lindeman RD. Overview: renal physiology and pathophysiology of aging. *Am J Kidney Dis* 1990; 16:275.
69. Giannelli SV, Patel KV, Windham BG, et al. Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. *J Am Geriatr Soc* 2007; 55:816.
70. Tsai KS, Heath H 3rd, Kumar R, Riggs BL. Impaired vitamin D metabolism with aging in women. Possible role in pathogenesis of senile osteoporosis. *J Clin Invest* 1984; 73:1668.
71. Kinyamu HK, Gallagher JC, Petranick KM, Ryschon KL. Effect of parathyroid hormone (hPTH[1-34]) infusion on serum 1,25-dihydroxyvitamin D and parathyroid hormone in normal women. *J Bone Miner Res* 1996; 11:1400.
72. Noth RH, Lassman MN, Tan SY, et al. Age and the renin-aldosterone system. *Arch Intern Med* 1977; 137:1414.
73. Weidmann P, De Myttenaere-Bursztein S, Maxwell MH, de Lima J. Effect on aging on plasma renin and aldosterone in normal man. *Kidney Int* 1975; 8:325.
74. Diz DI, Lewis K. Dahl memorial lecture: the renin-angiotensin system and aging. *Hypertension* 2008; 52:37.

75. Powers JS, Krantz SB, Collins JC, et al. Erythropoietin response to anemia as a function of age. *J Am Geriatr Soc* 1991; 39:30.
76. Drew DA, Katz R, Kritchevsky S, et al. Association between Soluble Klotho and Change in Kidney Function: The Health Aging and Body Composition Study. *J Am Soc Nephrol* 2017; 28:1859.
77. Fu A, Nair KS. Age effect on fibrinogen and albumin synthesis in humans. *Am J Physiol* 1998; 275:E1023.
78. Fleg JL, O'Connor F, Gerstenblith G, et al. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *J Appl Physiol* (1985) 1995; 78:890.
79. Taffet GE, Lakatta EG. Aging of the Cardiovascular System. In: Principles of Geriatric Medicine and Gerontology, 5th ed, Hazzard WR, Blass JP, Halter JB, et al (Eds), McGraw-Hill, New York 2003. p.403.
80. Wehrum T, Lodemann T, Hagenlocher P, et al. Age-related changes of right atrial morphology and inflow pattern assessed using 4D flow cardiovascular magnetic resonance: results of a population-based study. *J Cardiovasc Magn Reson* 2018; 20:38.
81. Van de Veire NR, De Backer J, Ascoop AK, et al. Echo-cardiographically estimated left ventricular end-diastolic and right ventricular systolic pressure in normotensive healthy individuals. *Int J Cardiovasc Imaging* 2006; 22:633.
82. Gates PE, Tanaka H, Graves J, Seals DR. Left ventricular structure and diastolic function with human ageing. Relation to habitual exercise and arterial stiffness. *Eur Heart J* 2003; 24:2213.
83. Zhang XP, Vatner SF, Shen YT, et al. Increased apoptosis and myocyte enlargement with decreased cardiac mass; distinctive features of the aging male, but not female, monkey heart. *J Mol Cell Cardiol* 2007; 43:487.
84. Kajstura J, Cheng W, Sarangarajan R, et al. Necrotic and apoptotic myocyte cell death in the aging heart of Fischer 344 rats. *Am J Physiol* 1996; 271:H1215.
85. Nathania M, Hollingsworth KG, Bates M, et al. Impact of age on the association between cardiac high-energy phosphate metabolism and cardiac power in women. *Heart* 2018; 104:111.
86. Piotrowska, Niezgoda M, lebkowski W, et al. Sex differences in distribution of cannabinoid receptors (CB1 and CB2), S100A6 and CacyBP/SIP in human ageing hearts. *Biol Sex Differ* 2018; 9:50.
87. Parati G, Di Rienzo M. Determinants of heart rate and heart rate variability. *J Hypertens* 2003; 21:477.
88. Fleg JL, Kennedy HL. Long-term prognostic significance of ambulatory electrocardiographic findings in apparently healthy subjects greater than or equal to 60 years of age. *Am J Cardiol* 1992; 70:748.
89. Busby MJ, Shefrin EA, Fleg JL. Prevalence and long-term significance of exercise-induced frequent or repetitive ventricular ectopic beats in apparently healthy volunteers. *J Am Coll Cardiol* 1989; 14:1659.
90. Kitzman DW, Scholz DG, Hagen PT, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. *Mayo Clin Proc* 1988; 63:137.
91. Hollingsworth KG, Blamire AM, Keavney BD, Macgowan GA. Left ventricular torsion, energetics, and diastolic function in normal human aging. *Am J Physiol Heart Circ Physiol* 2012; 302:H885.