MALİGN HİPERKALSEMİ TEDAVİSİ

Mustafa KARACA[1]

GİRİŞ

Hiperkalsemi kanser haslarında nispeten yaygın olup, olguların yaklaşık %20 -30'unde oluşmaktadır (1). Yatan hasta ortamında hiperkalseminin en yaygın nedenidir. Hem solid tümörleri hem de hematolojik maligniteleri bulunan hastalarda oluşur. Amerika Birleşik Devletleri'nde hiperkalsemi ile ilişkili en yaygın kanserler meme, renal ve akciğer kanseri ile multipl miyelomdur (2). Malignite genellikle hiperkalsemiye neden olduğu zaman klinik olarak belirgindir ve malignite hiperkalsemisi bulunan hastalarda prognoz sıklıkla kötüdür. Burada hiperkalsemi mekanizmaları,hiperkalseminin klinik belirtileri, tanısı ve tedavisi ayrı ayrı detaylı bir şekilde ele alınmaktadır.

Malign Hiperkalsemi Mekanizmaları

Malignite hiperkalsemisinin oluşabileceği üç temel mekanizma vardır (1, 3, 4):

- Paratiroid hormonla ilişkili proteinin (PTHrP) tümör sekresyonu
- Sitokinlerin (osteoklast aktive edici faktörler dahil) lokal salınımı ile osteolitik metastazlar
- 1, 25-dihidroksi vitamin D nin (kalsitriol) tümör üretimi.

[1] Doç. Dr., Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Antalya Sağlık Uygulama ve Araştırma Merkezi/İç Hastalıkları AD, drmkaraca07@gmail.com

oluşabilir. Bu tür hastalarda glikokortikoidler (örn. 20-40 mg/gün prednizon) genellikle 1-5 gün içinde akciğerlerdeki ve lenf nodlarındaki aktive mononükler hücreler tarafından kalsitriol üretimini azaltarak serum kalsiyom konsantrasyonlarını düşürür.

Diğer tedaviler

Denosumab, zoledronik aside (ZA) dirençli hiperkalsemili hastalar veya şiddetli böbrek yetmezliği nedeniyle bifosfonatların kontrendike olduğu hastalar için bir seçenektir. Özellikle bifosfonatlara rağmen inatçı hiperkalsemisi olan hastalarda, malignite hiperkalsemisinin tedavisi için denosumab kullanımına ilişkin artan sayıda olgu raporu ve olgu serileri bulunmaktadır (107-109)

KAYNAKLAR

1. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med 2005; 352:373.
2. Gastanaga VM, Schwartzberg LS, Jain RK, et al. Prevalence of hypercalcemia among cancer patients in the United States. Cancer Med 2016; 5:2091.
3. Clines GA, Guise TA. Hypercalcaemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis to bone. Endocr Relat Cancer 2005; 12:549.
4. Mirrakhimov AE. Hypercalcemia of Malignancy: An Update on Pathogenesis and Management. N Am J Med Sci 2015; 7:483.
5. Ratcliffe WA, Hutchesson AC, Bundred NJ, Ratcliffe JG. Role of assays for parathyroid-hormone-related protein in investigation of hypercalcaemia. Lancet 1992; 339:164.
6. Ikeda K, Ohno H, Hane M, et al. Development of a sensitive two-site immunoradiometric assay for parathyroid hormone-related peptide: evidence for elevated levels in plasma from patients with adult T-cell leukemia/lymphoma and B-cell lymphoma. J Clin Endocrinol Metab 1994; 79:1322.
7. Horwitz MJ, Tedesco MB, Sereika SM, et al. Direct comparison of sustained infusion of human parathyroid hormone-related protein-(1-36) [hPTHrP-(1-36)] versus hPTH-(1-34) on serum calcium, plasma 1,25-dihydroxyvitamin D concentrations, and fractional calcium excretion in healthy human volunteers. J Clin Endocrinol Metab 2003; 88:1603.
8. Horwitz MJ. Non-parathyroid hypercalcemia. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 9th ed, Bilezikian JP (Ed), Wiley-Blackwell, Hoboken, NJ 2018. p.639.
9. Wimalawansa SJ. Significance of plasma PTH-rp in patients with hypercalcemia of malignancy treated with bisphosphonate. Cancer 1994; 73:2223.

10. Pecherstorfer M, Schilling T, Blind E, et al. Parathyroid hormone-related protein and life expectancy in hypercalcemic cancer patients. J Clin Endocrinol Metab 1994; 78:1268.
11. Bhandari S, Kumar R, Tripathi P, et al. Outcomes of hypercalcemia of malignancy in patients with solid cancer: a national inpatient analysis. Med Oncol 2019; 36:90.
12. Roodman GD. Mechanisms of bone lesions in multiple myeloma and lymphoma. Cancer 1997; 80:1557.
13. Seymour JF, Grill V, Martin TJ, et al. Hypercalcemia in the blastic phase of chronic myeloid leukemia associated with elevated parathyroid hormone-related protein. Leukemia 1993; 7:1672.
14. Nakamura Y, Bando H, Shintani Y, et al. Serum parathyroid hormone-related protein concentrations in patients with hematologic malignancies or solid tumors. Acta Endocrinol (Copenh) 1992; 127:324.
15. Inoue D, Matsumoto T, Ogata E, Ikeda K. 22-Oxacalcitriol, a noncalcemic analogue of calcitriol, suppresses both cell proliferation and parathyroid hormone-related peptide gene expression in human T cell lymphotrophic virus, type I-infected T cells. J Biol Chem 1993; 268:16730.
16. Ishibashi K, Ishitsuka K, Chuman Y, et al. Tumor necrosis factor-beta in the serum of adult T-cell leukemia with hypercalcemia. Blood 1991; 77:2451.
17. Burtis WJ, Brady TG, Orloff JJ, et al. Immunochemical characterization of circulating parathyroid hormone-related protein in patients with humoral hypercalcemia of cancer. N Engl J Med 1990; 322:1106.
18. Rizzoli R, Ferrari SL, Pizurki L, et al. Actions of parathyroid hormone and parathyroid hormone-related protein. J Endocrinol Invest 1992; 15:51.
19. Fraher LJ, Hodsman AB, Jonas K, et al. A comparison of the in vivo biochemical responses to exogenous parathyroid hormone-(1-34) [PTH-(1-34)] and PTH-related peptide-(1-34) in man. J Clin Endocrinol Metab 1992; 75:417.
20. Esbrit P, Egido J. The emerging role of parathyroid hormone-related protein as a renal regulating factor. Nephrol Dial Transplant 2000; 15:1109.
21. Schilling T, Pecherstorfer M, Blind E, et al. Parathyroid hormone-related protein (PTHrP) does not regulate 1,25-dihydroxyvitamin D serum levels in hypercalcemia of malignancy. J Clin Endocrinol Metab 1993; 76:801.
22. Schweitzer DH, Hamdy NA, Frölich M, et al. Malignancy-associated hypercalcaemia: resolution of controversies over vitamin D metabolism by a pathophysiological approach to the syndrome. Clin Endocrinol (Oxf) 1994; 41:251.
23. Nakayama K, Fukumoto S, Takeda S, et al. Differences in bone and vitamin D metabolism between primary hyperparathyroidism and malignancy-associated hypercalcemia. J Clin Endocrinol Metab 1996; 81:607.
24. Horwitz MJ, Tedesco MB, Sereika SM, et al. Continuous PTH and PTHrP infusion causes suppression of bone formation and discordant effects on 1,25(OH)2 vitamin D. J Bone Miner Res 2005; 20:1792.
25. Syed MA, Horwitz MJ, Tedesco MB, et al. Parathyroid hormone-related protein-(1--36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy. J

Clin Endocrinol Metab 2001; 86:1525.
26. Mundy GR, Edwards JR. PTH-related peptide (PTHrP) in hypercalcemia. J Am Soc Nephrol 2008; 19:672.
27. Gurney H, Grill V, Martin TJ. Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcaemia. Lancet 1993; 341:1611.
28. Ling PJ, A'Hern RP, Hardy JR. Analysis of survival following treatment of tumour-induced hypercalcaemia with intravenous pamidronate (APD). Br J Cancer 1995; 72:206.
29. Quinn JM, Matsumura Y, Tarin D, et al. Cellular and hormonal mechanisms associated with malignant bone resorption. Lab Invest 1994; 71:465.
30. Grill V, Ho P, Body JJ, et al. Parathyroid hormone-related protein: elevated levels in both humoral hypercalcemia of malignancy and hypercalcemia complicating metastatic breast cancer. J Clin Endocrinol Metab 1991; 73:1309.
31. Legha SS, Powell K, Buzdar AU, Blumenschein GR. Tamoxifen-induced hypercalcemia in breast cancer. Cancer 1981; 47:2803.
32. Arumugam GP, Sundravel S, Shanthi P, Sachdanandam P. Tamoxifen flare hypercalcemia: an additional support for gallium nitrate usage. J Bone Miner Metab 2006; 24:243.
33. Valentin-Opran A, Eilon G, Saez S, Mundy GR. Estrogens and antiestrogens stimulate release of bone resorbing activity by cultured human breast cancer cells. J Clin Invest 1985; 75:726.
34. Kuroi K, Yamashita T, Aruga T, et al. Flare hypercalcemia after letrozole in a patient with liver metastasis from breast cancer: a case report. J Med Case Rep 2011; 5:495.
35. Järhult J. Anastrozole can cause severe hypercalcaemia mimicking primary hyperparathyroidism. Breast Cancer 2014; 21:379.
36. Terpos E, Christoulas D, Gavriatopoulou M. Biology and treatment of myeloma related bone disease. Metabolism 2018; 80:80.
37. Edwards CM, Silberman R. Myeloma bone disease and other hematological malignancies. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 9th ed, Bilezikian JP (Ed), Wiley-Blackwell, Hoboken, NJ 2018. p.760.
38. Seymour JF, Gagel RF. Calcitriol: the major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. Blood 1993; 82:1383.
39. Henderson JE, Shustik C, Kremer R, et al. Circulating concentrations of parathyroid hormone-like peptide in malignancy and in hyperparathyroidism. J Bone Miner Res 1990; 5:105.
40. Chukir T, Liu Y, Hoffman K, et al. Calcitriol Elevation Is Associated with a Higher Risk of Refractory Hypercalcemia of Malignancy in Solid Tumors. J Clin Endocrinol Metab 2020; 105.
41. Hibi M, Hara F, Tomishige H, et al. 1,25-dihydroxyvitamin D-mediated hypercalcemia in ovarian dysgerminoma. Pediatr Hematol Oncol 2008; 25:73.
42. Scheinman SJ, Kelberman MW, Tatum AH, Zamkoff KW. Hypercalcemia with excess serum 1,25 dihydroxyvitamin D in lymphomatoid granulomatosis/angiocentric lymphoma. Am J Med Sci 1991; 301:178.
43. Shivnani SB, Shelton JM, Richardson JA, Maalouf NM. Hypercalcemia of malignan-

cy with simultaneous elevation in serum parathyroid hormone--related peptide and 1,25-dihydroxyvitamin D in a patient with metastatic renal cell carcinoma. Endocr Pract 2009; 15:234.
44. Yoshimoto K, Yamasaki R, Sakai H, et al. Ectopic production of parathyroid hormone by small cell lung cancer in a patient with hypercalcemia. J Clin Endocrinol Metab 1989; 68:976.
45. Nussbaum SR, Gaz RD, Arnold A. Hypercalcemia and ectopic secretion of parathyroid hormone by an ovarian carcinoma with rearrangement of the gene for parathyroid hormone. N Engl J Med 1990; 323:1324.
46. Strewler GJ, Budayr AA, Clark OH, Nissenson RA. Production of parathyroid hormone by a malignant nonparathyroid tumor in a hypercalcemic patient. J Clin Endocrinol Metab 1993; 76:1373.
47. Nielsen PK, Rasmussen AK, Feldt-Rasmussen U, et al. Ectopic production of intact parathyroid hormone by a squamous cell lung carcinoma in vivo and in vitro. J Clin Endocrinol Metab 1996; 81:3793.
48. Wong K, Tsuda S, Mukai R, et al. Parathyroid hormone expression in a patient with metastatic nasopharyngeal rhabdomyosarcoma and hypercalcemia. Endocrine 2005; 27:83.
49. VanHouten JN, Yu N, Rimm D, et al. Hypercalcemia of malignancy due to ectopic transactivation of the parathyroid hormone gene. J Clin Endocrinol Metab 2006; 91:580.
50. Vacher-Coponat H, Opris A, Denizot A, et al. Hypercalcaemia induced by excessive parathyroid hormone secretion in a patient with a neuroendocrine tumour. Nephrol Dial Transplant 2005; 20:2832.
51. Kandil E, Noureldine S, Khalek MA, et al. Ectopic secretion of parathyroid hormone in a neuroendocrine tumor: a case report and review of the literature. Int J Clin Exp Med 2011; 4:234.
52. Nakajima K, Tamai M, Okaniwa S, et al. Humoral hypercalcemia associated with gastric carcinoma secreting parathyroid hormone: a case report and review of the literature. Endocr J 2013; 60:557.
53. Hutchesson AC, Bundred NJ, Ratcliffe WA. Survival in hypercalcaemic patients with cancer and co-existing primary hyperparathyroidism. Postgrad Med J 1995; 71:28.
54. Strodel WE, Thompson NW, Eckhauser FE, Knol JA. Malignancy and concomitant primary hyperparathyroidism. J Surg Oncol 1988; 37:10.
55. Casez J, Pfammatter R, Nguyen Q, et al. Diagnostic approach to hypercalcemia: relevance of parathyroid hormone and parathyroid hormone-related protein measurements. Eur J Intern Med 2001; 12:344.
56. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266.
57. Bilezikian JP. Clinical review 51: Management of hypercalcemia. J Clin Endocrinol Metab 1993; 77:1445.
58. Bilezikian JP. Management of acute hypercalcemia. N Engl J Med 1992; 326:1196.
59. Maier JD, Levine SN. Hypercalcemia in the Intensive Care Unit: A Review of Pathophysiology, Diagnosis, and Modern Therapy. J Intensive Care Med 2015; 30:235.
60. Fatemi S, Singer FR, Rude RK. Effect of salmon calcitonin and etidronate on hypercalcemia of malignancy. Calcif Tissue Int 1992; 50:107.

61. Selby PL, Davies M, Marks JS, Mawer EB. Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate. Clin Endocrinol (Oxf) 1995; 43:531.
62. Hosking DJ, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. Q J Med 1981; 50:473.
63. Suki WN, Yium JJ, Von Minden M, et al. Acute treatment of hypercalcemia with furosemide. N Engl J Med 1970; 283:836.
64. Body JJ. Hypercalcemia of malignancy. Semin Nephrol 2004; 24:48.
65. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. Ann Intern Med 2008; 149:259.
66. Austin LA, Heath H 3rd. Calcitonin: physiology and pathophysiology. N Engl J Med 1981; 304:269.
67. Deftos LJ, First BP. Calcitonin as a drug. Ann Intern Med 1981; 95:192.
68. Dumon JC, Magritte A, Body JJ. Nasal human calcitonin for tumor-induced hypercalcemia. Calcif Tissue Int 1992; 51:18.
69. Wisneski LA. Salmon calcitonin in the acute management of hypercalcemia. Calcif Tissue Int 1990; 46 Suppl:S26.
70. Vaughn CB, Vaitkevicius VK. The effects of calcitonin in hypercalcemia in patients with malignancy. Cancer 1974; 34:1268.
71. Ljunghall S. Use of clodronate and calcitonin in hypercalcemia due to malignancy. Recent Results Cancer Res 1989; 116:40.
72. Chevallier B, Peyron R, Basuyau JP, et al. [Human calcitonin in neoplastic hypercalcemia. Results of a prospective randomized trial]. Presse Med 1988; 17:2375.
73. Carano A, Teitelbaum SL, Konsek JD, et al. Bisphosphonates directly inhibit the bone resorption activity of isolated avian osteoclasts in vitro. J Clin Invest 1990; 85:456.
74. Ryzen E, Martodam RR, Troxell M, et al. Intravenous etidronate in the management of malignant hypercalcemia. Arch Intern Med 1985; 145:449.
75. Singer FR, Ritch PS, Lad TE, et al. Treatment of hypercalcemia of malignancy with intravenous etidronate. A controlled, multicenter study. The Hypercalcemia Study Group. Arch Intern Med 1991; 151:471.
76. Gucalp R, Ritch P, Wiernik PH, et al. Comparative study of pamidronate disodium and etidronate disodium in the treatment of cancer-related hypercalcemia. J Clin Oncol 1992; 10:134.
77. Gucalp R, Theriault R, Gill I, et al. Treatment of cancer-associated hypercalcemia. Double-blind comparison of rapid and slow intravenous infusion regimens of pamidronate disodium and saline alone. Arch Intern Med 1994; 154:1935.
78. Rizzoli R, Thiébaud D, Bundred N, et al. Serum parathyroid hormone-related protein levels and response to bisphosphonate treatment in hypercalcemia of malignancy. J Clin Endocrinol Metab 1999; 84:3545.
79. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001; 19:558.
80. Berenson JR. Treatment of hypercalcemia of malignancy with bisphosphonates. Semin Oncol 2002; 29:12.

81. Body JJ, Bartl R, Burckhardt P, et al. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. J Clin Oncol 1998; 16:3890.
82. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med 2005; 352:373.
83. Schwartz LM, Woloshin S. Lost in transmission--FDA drug information that never reaches clinicians. N Engl J Med 2009; 361:1717.
84. Massagli TL, Cardenas DD. Immobilization hypercalcemia treatment with pamidronate disodium after spinal cord injury. Arch Phys Med Rehabil 1999; 80:998.
85. Jansson S, Tisell LE, Lindstedt G, Lundberg PA. Disodium pamidronate in the preoperative treatment of hypercalcemia in patients with primary hyperparathyroidism. Surgery 1991; 110:480.
86. Mark S. Hypercalcaemia in an immobilised patient with pneumonia. Br J Clin Pract 1995; 49:327.
87. McIntyre HD, Cameron DP, Urquhart SM, Davies WE. Immobilization hypercalcaemia responding to intravenous pamidronate sodium therapy. Postgrad Med J 1989; 65:244.
88. Gibbs CJ, Peacock M. Hypercalcaemia due to sarcoidosis corrects with bisphosphonate treatment. Postgrad Med J 1986; 62:937.
89. Ralston SH, Gallacher SJ, Patel U, et al. Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. Lancet 1989; 2:1180.
90. Sawyer N, Newstead C, Drummond A, Cunningham J. Fast (4-h) or slow (24-h) infusions of pamidronate disodium (aminohydroxypropylidene diphosphonate (APD)) as single shot treatment of hypercalcaemia. Bone Miner 1990; 9:121.
91. Nussbaum SR, Younger J, Vandepol CJ, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. Am J Med 1993; 95:297.
92. Wimalawansa SJ. Optimal frequency of administration of pamidronate in patients with hypercalcaemia of malignancy. Clin Endocrinol (Oxf) 1994; 41:591.
93. Gurney H, Grill V, Martin TJ. Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcaemia. Lancet 1993; 341:1611.
94. Walls J, Ratcliffe WA, Howell A, Bundred NJ. Response to intravenous bisphosphonate therapy in hypercalcaemic patients with and without bone metastases: the role of parathyroid hormone-related protein. Br J Cancer 1994; 70:169.
95. Wimalawansa SJ. Significance of plasma PTH-rp in patients with hypercalcemia of malignancy treated with bisphosphonate. Cancer 1994; 73:2223.
96. Ralston SH, Thiébaud D, Herrmann Z, et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. Br J Cancer 1997; 75:295.
97. Pecherstorfer M, Herrmann Z, Body JJ, et al. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. J Clin Oncol 1996; 14:268.
98. Pecherstorfer M, Steinhauer EU, Rizzoli R, et al. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. Support Care Cancer 2003; 11:539.

99. O'Rourke NP, McCloskey EV, Vasikaran S, et al. Effective treatment of malignant hypercalcaemia with a single intravenous infusion of clodronate. Br J Cancer 1993; 67:560.
100. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. Ann Oncol 2006; 17:897.
101. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. Drug Saf 1999; 21:389.
102. Edwards BJ, Sun M, West DP, et al. Incidence of Atypical Femur Fractures in Cancer Patients: The MD Anderson Cancer Center Experience. J Bone Miner Res 2016; 31:1569.
103. Henrich D, Hoffmann M, Uppenkamp M, Bergner R. Ibandronate for the treatment of hypercalcemia or nephrocalcinosis in patients with multiple myeloma and acute renal failure: Case reports. Acta Haematol 2006; 116:165.
104. Machado CE, Flombaum CD. Safety of pamidronate in patients with renal failure and hypercalcemia. Clin Nephrol 1996; 45:175.
105. Trimarchi H, Lombi F, Forrester M, et al. Disodium pamidronate for treating severe hypercalcemia in a hemodialysis patient. Nat Clin Pract Nephrol 2006; 2:459.
106. Davenport A, Goel S, Mackenzie JC. Treatment of hypercalcaemia with pamidronate in patients with end stage renal failure. Scand J Urol Nephrol 1993; 27:447.
107. Dietzek A, Connelly K, Cotugno M, et al. Denosumab in hypercalcemia of malignancy: a case series. J Oncol Pharm Pract 2015; 21:143.
108. Karuppiah D, Thanabalasingham G, Shine B, et al. Refractory hypercalcaemia secondary to parathyroid carcinoma: response to high-dose denosumab. Eur J Endocrinol 2014; 171:K1.
109. Adhikaree J, Newby Y, Sundar S. Denosumab should be the treatment of choice for bisphosphonate refractory hypercalcaemia of malignancy. BMJ Case Rep 2014; 2014.