

# KANSERDE HİPERTANSİYON YÖNETİMİ

**8.**

## BÖLÜM

Hızır OKUYAN<sup>1</sup>

### I. GİRİŞ

Modern kanser tedavileri ile birçok kanser kür olabilmekte fakat kür olmayan kanserler de kronik hastalık olarak tedavi edilmektedirler. Dünya genelinde bu kronik hastalık sınıfında çok sayıda hasta mevcut olup, giderek de bu hasta populasyonu artmaktadır. Kanser tanısı alan hasta sayısı Amerika Birleşik Devletler'in de 1970'lerde yaklaşık üç milyon iken 2019'da yaklaşık on yedi milyona artmıştır.

<sup>1</sup> Bu hastalarda genel populasyon ile kıyaslandığında kardiyovasküler risk (hipertansiyon, hiperlipidemi, diyabetes mellitus, obezite), kardiyovasküler hastalık<sup>2-4</sup> ve pulmoner hastalık insidansında artış gözlenmiştir.<sup>5,6</sup> Hipertansiyon kronik böbrek hastalığı, kardiyovasküler hastalık ve kanser; sigara, diyabetes mellitus ve obezite gibi ortak risk faktörlerine sahiptir. Buna paralel olarak yapılan çeşitli çalışmalar da hipertansiyonun renal kanser, ağız, gırtlak ve yemek borusu kanseri ve meme kanseri için risk faktörü olduğu gösterilmiştir.<sup>7-9</sup> Kanser hastalarında en sık eşlik eden kardiyovasküler hastalık hipertansiyondur.<sup>10</sup> Çeşitli kanserler hipertansiyon gelişimine ya da mevcut hipertansiyon kliniğinde kötüleşmeye neden olabilmektedir. Ayrıca kanser tedavisi için kullanılan bazı ilaçlar, direkt olarak veya mikroanjiyopatik ve nefrotoksik etkileri aracılığı ile dolaylı olarak hipertansiyona neden olmaktadır. Kemoterapi alan kanser hastalarında hipertansiyon gelişmesi en ciddi yan etkilerden biridir. Yaklaşık 25000 solid malign tümörlü hastadan oluşan retrospektif bir analizde ücste bir hastada yeni başlığılı hipertansiyon gelişmesi izlenmiştir.<sup>11</sup> Orta derecede hipertansiyon (150-160/100-110 mmHg) gelişme oranı en sık renal kanserde, ciddi hipertansiyon (160-180/110-120 mmHg) gastrik kanserlerde, kriz seviyesinde hipertansiyon (>180/120 mmHg) gelişmesi ise en sık oranda over kanserlerinde görülmüştür. İlk kanser tanısı konulmasından hipertansiyona kadar ortalama zaman 96 gündür. Hipertansiyon gelişiminde ke-

<sup>1</sup> Uzm. Dr., Kardiyoloji Kliniği, hizirokuyan@gmail.com ORCID iD: 0000-0001-5091-1687

etmekte, bu nedenle klinik uygulamada kullanılması istenmeyen farmakokinetik etkileşime neden olabilmektedir.<sup>84</sup> Psikolojik stres ve ağrı sempatik sistem aktivasyonu aracılığı ile hipertansiyonu kötülestirebilmektedir. Kronik ağrının artmış hipertansiyon riski ile ilişkili olabileceği saptanmıştır.<sup>85</sup> Bu nedenle kronik ağrı uygun bir şekilde tedavi edilmeli kontrol altına alınmalıdır.<sup>13</sup>

Sonuç olarak, ACE inhibitörleri, ARB'ler ve dihidropiridin olmayan CCB'ler, kemoterapiye bağlı hipertansiyon için ilk tercih edilen ilaçlar olarak kabul edilmektedir.<sup>13</sup> Beta-blokerlerin ise özellikle sol ventrikül sistolik disfonksiyonu olan veya bundan dolayı yüksek risk altında olan hastalarda ACE inhibitörleri veya ARB'ler ile kombinasyon halinde kullanılması faydalı olabilir.<sup>13</sup> Olumlu bir hemodinamik profile sahip olduğundan ve NO biyoyararlanımını geri kazanabildiğinden<sup>75,86</sup> nebivolol tercih edilebilir. Diğer vazodilatator beta-blokerler de seçenek olarak kabul edilebilir.<sup>87</sup> Kemoterapinin kanser üzerinde olumlu bir etkisi olabilmekte; bu nedenle hipertansiyon nedeni ile kemoterapi tedavisinin kesilmesi nadiren olabilir. Yaşamı tehdit edebilen hipertansif kriz, posterior geri dönüşümlü encefalopati sendromu (PRES) ve hipertansif encefalopati durumlarında kemoterapi kesilmesi düşünülmelidir. Tibbi tedaviye rağmen kan basıncı kontrolü sağlanamamış ise kardiyovasküler istenmeyen olayların riski ve kemoterapinin faydası iyi tartılmalı ve ona göre karar verilmelidir. Antineoplastik ilaçların geçici olarak kesilmesi veya dozunun düşürülmesi hipertansif kriz durumlarında ve hastanın hipertansiyona bağlı istenmeyen majör kardiyovasküler olaylarda düşünülebilir.<sup>14,88</sup>

## V. SONUÇ

Kanser tanısı alıp kronik olarak takip edilen hasta popülasyonu artmaktadır. Kanserli hastalarda hipertansiyon sikliği normal popülasyona göre daha fazladır. Hipertansiyon istenmeyen kardiyovasküler olaylar için en yüksek risk faktörünü oluşturmaktadır. Bu nedenle tüm kanserli hastalar sağlıklı bireylerde olduğu gibi toplam kardiyovasküler risk açısından değerlendirilmelidir. Özellikle kemoterapi başlanması öncesi bu değerlendirme önemlidir. Hastanın tam değerlendirme yapıılırken başlangıç kan basıncı mutlaka ölçülmeli ve kayıt altına alınmalıdır. Özellikle hem hasta kaynaklı hem kullanılacak kemoterapi ve primer tümörün hipertansiyon için risk içermesi durumu varsa yakın kan basıncı takibi yapılmalıdır. Bu takip hastanın kendi ev ölçümleri ile ya da her tedavi döneminde ambulatuvar kan basıncı monitorizasyonu ile yapılabilir. Düzeltilebilir en önemli risk faktörü olan hipertansiyonun tanı ve tedavisi istenmeyen kardiyovasküler olayları önlemekle kalmayıp, ek olarak hastanın hayat kalitesini artıracaktır.

## KAYNAKÇA

- Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69(5):363-385.

2. Armenian SH, Xu L, Ky B, et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J Clin Oncol.* 2016;34(10):1122-1130.
3. Bates JE, Howell RM, Liu Q, et al. Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study. *J Clin Oncol.* 2019;37(13):1090-1101.
4. Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet.* 2019;394(10203):1041-1054.
5. Van Laar M, Feltbower RG, Gale CP, et al. Cardiovascular sequelae in long-term survivors of young peoples' cancer: a linked cohort study. *Br J Cancer.* 2014;110(5):1338-1341.
6. Flerlage JE, Kelly KM, Beishuizen A, et al. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CA-YAHL): Methodology statement. *Pediatr Blood Cancer.* 2017;64(7):10.1002/pbc.26421.
7. Colt JS, Schwartz K, Graubard BI, et al. Hypertension and risk of renal cell carcinoma among white and black Americans. *Epidemiology.* 2011;22:797-804.
8. Seo JH, Kim YD, Park CS, et al. Hypertension is associated with oral, laryngeal, and esophageal cancer: a nationwide population-based study. *Scientific Reports.* 2020 Jun;10(1):10291.
9. Han H, Guo W, Shi W, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. *Sci Rep.* 2017;7:44877.
10. Izzedine H, Ederhy S, Goldwasser F, et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol.* 2009;20(5):807-815.
11. Fraeman KH, Nordstrom BL, Luo W, et al. Incidence of new-onset hypertension in cancer patients: a retrospective cohort study. *Int J Hypertens.* 2013;2013:379252.
12. Gibson TM, Li Z, Green DM, et al. Blood Pressure Status in Adult Survivors of Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2017;26(12):1705-1713.
13. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37:2768-2801.
14. Maitland ML, Bakris GL, Black HR, et al. Cardiovascular Toxicities Panel, Convened by the Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst* 2010; 102:596-604.
15. Braithwaite D, Tammemagi CM, Moore DH, et al. Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. *Int J Cancer.* 2009; 124:1213-1219.
16. Dyer AR, Stamler J, Berkson DM, et al. High bloodpressure: a risk factor for cancer mortality? *Lancet* 1975; 1:1051-1056.
17. Park SM, Lim MK, Shin SA, et al. Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. *J Clin Oncol* 2006; 24:5017-5024.
18. Małyszko J, Małyszko M, Kozłowski L, et al. Hypertension in malignancy-an underappreciated problem. *Oncotarget.* 2018; 9:20855-20871.
19. Sagstuen H, Aass N, Fosså SD, et al. Blood pressure and body mass index in long-term survivors of testicular cancer. *J Clin Oncol.* 2005;23(22):4980-4990.
20. Yeh ET. Cardiotoxicity induced by chemotherapy and antibody therapy. *Annu Rev Med* 2006; 57:485-498.
21. Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. *Cancer Treat Rev* 2011; 37:300-311.
22. Pivot X, Schneeweiss A, Verma S, et al. Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic

- breast cancer: results from AVADO. *Eur J Cancer* 2011; 47:2387–2395.
- 23. Li W, Croce K, Steensma DP, McDermott DF, et al. Vascular and Metabolic Implications of Novel Targeted Cancer Therapies: Focus on Kinase Inhibitors. *J Am Coll Cardiol* 2015; 66:1160–78.
  - 24. Pinkhas D, Ho T, Smith S. Assessment of pazopanib-related hypertension, cardiac dysfunction and identification of clinical risk factors for their development. *Cardiooncology* 2017;3:5.
  - 25. Jurca SJ, Elliott WJ. Common Substances That May Contribute to Resistant Hypertension, and Recommendations for Limiting Their Clinical Effects. *Curr Hypertens Rep.* 2016;18(10):73.
  - 26. Madeddu P. Therapeutic angiogenesis and vasculogenesis for tissue regeneration. *Exp Physiol* 2005;90:315–26.
  - 27. Pandey AK, Singhi EK, Arroyo JP, et al. Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-associated hypertension and vascular disease. *Hypertension* 2018;71:e1–8.
  - 28. Lankhorst S, Danser AH, van den Meiracker AH. Endothelin-1 and antiangiogenesis. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R230–4.
  - 29. Vigneau C, Lorcy N, Dolley-Hitze T, et al. All anti-vascular endothelial growth factor drugs can induce 'pre-eclampsia-like syndrome': a RARE study. *Nephrol Dial Transplant* 2014;29:325–32.
  - 30. Basu A, Krishnamurthy S. Cellular responses to Cisplatin-induced DNA damage. *J Nucleic Acids*. 2010;2010:201367.
  - 31. Soultati A, Mountzios G, Avgerinou C, et al. Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications. *Cancer Treat Rev* 2012; 38:473–483.
  - 32. Kirchmair R, Walter DH, Ii M, et al. Antiangiogenesis mediates cisplatin-induced peripheral neuropathy: attenuation or reversal by local vascular endothelial growth factor gene therapy without augmenting tumor growth. *Circulation*. 2005; 111:2662–70.
  - 33. Jansson T, Persson E. Placental transfer of glucose and amino acids in intrauterine growth retardation: studies with substrate analogs in the awake guinea pig. *Pediatr Res.* 1990; 28:203– 8.
  - 34. El-Awady el-SE, Moustafa YM, Abo-Elmatty DM, et al. Cisplatin-induced cardiotoxicity: Mechanisms and cardioprotective strategies. *Eur J Pharmacol.* 2011; 650:335–41.
  - 35. Haugnes HS, Wethal T, Aass N, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. *J Clin Oncol.* 2010; 28:4649–57.
  - 36. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* 1979; 91:710–7.
  - 37. Hershman DL, McBride RB, Eisenberger A, et al. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2008; 26:3159–65.
  - 38. Jain M, Townsend RR. Chemotherapy agents and hypertension: a focus on angiogenesis blockade. *Curr Hypertens Rep.* 2007; 9:320–8.
  - 39. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol.* 2007; 25:3808–15.
  - 40. Saif MW, Xyla V, Makrilia N, et al. Thrombotic microangiopathy associated with gemcitabine: rare but real. *Expert Opin Drug Saf.* 2009;8(3):257-260.
  - 41. Bruno G, Bringhen S, Maffei I, et al. Cardiovascular Organ Damage and Blood Pressure Levels Predict Adverse Events in Multiple Myeloma Patients Undergoing Carfilzomib Therapy. *Cancers (Basel).* 2019;11(5):622.
  - 42. Wei Q, Xia Y. Proteasome inhibition down-regulates endothelial nitric-oxide synthase phosphorylation and function. *J Biol Chem.* 2006;281(31):21652-21659.
  - 43. Chen-Scarabelli C, Corsetti G, Pasini E, et al. Spasmogenic Effects of the Proteasome Inhibitor Carfilzomib on Coronary Resistance, Vascular Tone and Reactivity. *EBioMedicine.* 2017;21:206-212.
  - 44. Jubb AM, Hurwitz HI, Bai W et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. *J Clin Oncol* 2006; 24: 217–227.
  - 45. Zhu X, Wu S, Dahut WL et al. Risks of proteinuria and hypertension with bevacizumab, an

- antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007; 49: 186–193.
- 46. Mourad JJ, des Guetz G, Debbabi H, et all. Blood pressure rise following angiogenesis inhibition by bevacizumab. A crucial role for microcirculation. *Ann Oncol* 2008; 19: 927–934.
  - 47. Hamnvik OP, Choueiri TK, Turchin A, et al. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer*. 2015;121(2):311-319.
  - 48. Abi Aad S, Pierce M, Barmaimon G, et al. Hypertension induced by chemotherapeutic and immunosuppressive agents: a new challenge. *Crit Rev Oncol Hematol* 2015; 93:28–35.
  - 49. Takeda Y, Yoneda T, Ito Y, et al. Stimulation of endothelin mRNA and secretion in human endothelial cells by FK 506. *J Cardiovasc Pharmacol*. 1993;22(suppl 8):S310–S312.
  - 50. Takeda Y, Miyamori I, Furukawa K, et al. Mechanisms of FK 506-induced hypertension in the rat. *Hypertension*. 1999;33(1):130-136.
  - 51. Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *Bosentan Hypertension Investigators*. *N Engl J Med*. 1998;338(12):784-790.
  - 52. Pufall MA. Glucocorticoids and Cancer. *Adv Exp Med Biol*. 2015;872:315-333.
  - 53. Baum M, Moe OW. Glucocorticoid-mediated hypertension: does the vascular smooth muscle hold all the answers? *J Am Soc Nephrol* 2008; 19:1251–1253.
  - 54. Krapf R, Hulter HN. Arterial hypertension induced by erythropoietin and erythropoiesis-stimulating agents (ESA). *Clin J Am Soc Nephrol* 2009; 4:470–480.
  - 55. Souza VB, Silva EN, Ribeiro ML, Martins Wde A. Hypertension in patients with cancer. *Arq Bras Cardiol* 2015; 104:246–252.
  - 56. Meacham LR, Chow EJ, Ness KK, et al. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev* 2010; 19:170–181.
  - 57. Fakhouri F, La Batie Alanore A, Rérolle JP, et al. Presentation and revascularization outcomes in patients with radiation-induced renal artery stenosis. *Am J Kidney Dis*. 2001;38(2):302-309.
  - 58. Meacham LR, Chow EJ, Ness KK, et al. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev* 2010; 19:170–181.
  - 59. Spiro SG, Gould MK, Colice GL; American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):149S-160S.
  - 60. Nathanson L, Hall TC: Introduction: paraneoplastic syndromes. *Semin Oncol* 1997;24:265-8.
  - 61. H. Arai, S. Saitoh, T. Matsumoto, et al. Hypertension as a paraneoplastic syndrome in hepatocellular carcinoma. *J Gastroenterol*, 34 (1999), pp. 530–534.
  - 62. Kew MC, Leckie BJ, Greeff MC. Arterial Hypertension as a Paraneoplastic Phenomenon in Hepatocellular Carcinoma. *Arch Intern Med*. 1989;149(9):2111–2113.
  - 63. Beard CM, Sheps SG, Kurland LT, et al. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc*. 1983;58(12):802-804.
  - 64. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(6):1915-1942.
  - 65. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med*. 1990;322(17):1195-1201.
  - 66. Veron Esquivel D, Batiz F, Farias Vega A, et al. Adrenocortical carcinoma, an unusual cause of secondary hypertension. *BMJ Case Rep*. 2016;2016:bcr2016217918. Published 2016 Dec 7.
  - 67. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–104.
  - 68. Virizuela JA, García AM, de Las Peñas R, et al. SEOM clinical guidelines on cardiovascular toxicity (2018). *Clin Transl Oncol*. 2019;21(1):94-105.

69. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335–2342.
70. Ahmad T, Eisen T. Kinase inhibition with BAY 43-9006 in renal cell carcinoma. *Clin Cancer Res* 2004; 10 (18 Pt 2):6388S–6392S.
71. Biagi JJ, Oza AM, Chalchal HI, et al. A phase II study of sunitinib in patients with recurrent epithelial ovarian and primary peritoneal carcinoma: an NCIC Clinical Trials Group Study. *Ann Oncol* 2011; 22:335–340.
72. Borthakur G, Kantarjian H, Ravandi F, et al. Phase I study of sorafenib in patients with refractory or relapsed acute leukemias. *Haematologica* 2011; 96:62–68.
73. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2005; 23:8033–8040.
74. Rixe O, Bukowski RM, Michaelson MD, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. *Lancet Oncol* 2007; 8:975–984.
75. Copur MS, Obermiller A. An algorithm for the management of hypertension in the setting of vascular endothelial growth factor signaling inhibition. *Clin Colorectal Cancer* 2011; 10:151–156.
76. Khakoo AY, Sidman RL, Pasqualini R, et al. Does the renin angiotensin system participate in regulation of human vasculogenesis and angiogenesis? *Cancer Res* 2008; 68:9112–9115.
77. Dincer M, Altundag K. Angiotensin-converting enzyme inhibitors for bevacizumab-induced hypertension. *Ann Pharmacother* 2006; 40:2278–2279.
78. Keizman D, Huang P, Eisenberger MA, et al. Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: a retrospective examination. *Eur J Cancer* 2011; 47:1955–1961.
79. Cameron AC, Touyz RM, Lang NN. Vascular complications of cancer chemotherapy. *Can J Cardiol* 2016; 32:852–862.
80. Langenberg MH, van Herpen CM, De Bono J, et al. Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: results from a phase II randomized, factorial, double-blind study of Cediranib in patients with advanced solid tumors. *J Clin Oncol* 2009; 27:6152–6159.
81. Curwen JO, Musgrave HL, Kendrew J, et al. Inhibition of vascular endothelial growth factor-a signaling induces hypertension: examining the effect of cediranib (recentin; AZD2171) treatment on blood pressure in rat and the use of concomitant antihypertensive therapy. *Clin Cancer Res* 2008; 14:3124–3131.
82. Albert DH, Tapang P, Magoc TJ, et al. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. *Mol Cancer Ther*. 2006;5(4):995–1006.
83. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. *Hypertension*. 2018;72(5):e53–e90.
84. Lankhorst S, Kappers MH, van Esch JH, et al. Treatment of hypertension and renal injury induced by the angiogenesis inhibitor sunitinib: preclinical study. *Hypertension* 2014; 64:1282–1289.
85. Bruehl S, Chung OY, Jirjis JN, et al. Prevalence of clinical hypertension in patients with chronic pain compared to nonpain general medical patients. *Clin J Pain*. 2005;21(2):147-153.
86. Kamp O, Metra M, Bugatti S, et al. Nebivolol: haemodynamic effects and clinical significance of combined beta-blockade and nitric oxide release. *Drugs* 2010; 70:41–56.
87. Hashim D, Boffetta P, La Vecchia C, et al. The global decrease in cancer mortality: trends and disparities. *Ann Oncol* 2016; 27:926–933.
88. Escalante CP, Zalpour A. Vascular endothelial growth factor inhibitör induced hypertension: basics for primary care providers. *Cardiol Res Pract* 2011; 2011:816897.