KEMOTERAPİ İLİŞKİLİ EKG DEĞİŞİKLİKLERİ

2. BÖLÜM

Gizem ÇABUK[1]

GİRİŞ

Kanser tedavilerindeki gelişmeler hastaların sağ kalımını arttırmıştır ancak özellikle kardiyovasküler yan etkilerine bağlı mortalite ve morbidite önemli bir sorun teşkil etmektedir. Kanser tedavilerinin kardiyak yan etkileri kalp yapı ve fonksiyonuna olumsuz etki (kalp yetersizliği ve kalp kapak hastalıkları), kardiyovasküker hastalık gelişimini hızlandırma, arteryel hipertansiyon, pulmoner hipertansiyon, perikardiyal komplikasyonlar, tromboembolik ve aritmik yan etkiler olarak sınıflandırılabilir (1,2).

Kanser tedavisi ile ilişkili kardiyotoksisite kardiyoloji ve onkolojinin multidisipliner yaklaşımını gerektirir. Hastaların takibinde elektrokardiyografi (EKG) önemli bir rol oynamaktadır. Bu bölümde kemoterapötiklerin EKG üzerine etkilerinin değerlendirilmesi planlanmıştır.

1. MİYOKARDİYAL DİSFONKSİYON VE KALP YETERSİZLİĞİ

Miyokardiyal toksisiteyi tanımada tedavi öncesi ve tedavi süresince EKG değerlendirilmesi gerekmektedir. İstirahat taşikardisi, ST-T dalga değişiklikleri, ileti defektleri, QT uzaması ve aritmiler (ventriküler prematür kontraksiyonlar (VPS) ve atriyal prematür kontraksiyonlar (APS)) kardiyotoksisite konusunda fikir verebilmektedir ancak bu değişiklikler genellikle non-spesifik ve geçicidir (1,3)

2. KORONER ARTER HASTALIĞI

Fluoropirimidinler (5-FU), platinyum bileşenleri (sisplatin), VEGF inhbitörleri (bevacizumab, sorafenib) endotelyal hasar, vazospazm, prokoagülan etki ve arteriyel trombozu arttırıcı etki ile koroner arter hastalığına neden olabilirler.

[1] Sağlık Bilimleri Üniversitesi İzmir Tepecik Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği, giizemcelik@gmail.com. ORCID iD: 0000-0002-3478-4611

12. Topoizomeraz İnhibitörleri

Amsacrine QT intervalini uzatır ve non-spesifik ST/T dalga değişikliklerine, atriyal taşikardi, AF, ventriküler taşiaritmiler ve ani kardiyak ölüme neden olabilir (94-100). Dikkat çekici olarak ciddi kardiyak artimi gözlenen hastaların %37'sinde hipokalemi gözlenmiştir. Amsacrine kardiyak repolarizasyona olan etkisi ile aritmi riskini arttırmaktadır (101).

13. Tirozin Kinaz İnhibitörleri

Tirozin kinaz inhibitörleri akut koroner sendrom, sistemik hipertansiyon, sol ventrikül disfonksiyonu, kalp yetersizliği ve kardiyak aritmilere neden olabilir. Birçok protein kinaz inhibitörü (crizotinib, dasatinib, gefitinib, nilotinib, sorafenib, sunitinib, vandetanib, vemurafenib) hERG kanallarını inhibe eder ve aksiyon potansiyeli süresini ve QT intervalini uzatır (102, 103) ancak torsades de pointes riski <%1'dir. (5,8) Sorafenib ve sunitinib ile AF, (104-107) ponatinib ve crizotinib ile semptomatik bradikardi vakaları görülmüştür (108).

KAYNAKLAR

1. 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) *European Heart Journal* (2016) 37, 2768–2801.
2. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol* 2013;31:3673–3680.
3. Schmitz KH, Prosnitz RG, Schwartz,et al. Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer 118* (Suppl 8): S2270S2276, 2012
4. Tamargo J, Caballero R, Delpon E. Cancer chemotherapy and cardiac arrhythmias: a review. *Drug Saf*. 2015 Feb;38(2): 129-52.
5. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53:2231–2247.
6. Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. *Oncologist* 2013;18:900–908.
7. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf* 2013;36:295–316.
8. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. *J Clin Oncol* 2007;25:3362–3371.
9. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol* 2014;63:945–953.
10. Cazin B, Gorin NC, Laporte JP, et al. Cardiac complications after bone marrow transplantation. A report on a series of 63 consecutive transplantations. *Cancer.* 1986;57(10):2061–9.
11. Kupari M, Volin L, Suokas A, et al. Cardiac involvement in bone marrow transplantation: electrocardiographic changes, arrhythmias, heart failure and autopsy findings. *Bone Marrow Transplant.* 1990;5(2):91–8.
12. Gottdiener JS, Appelbaum FR, Ferrans VJ, et al. Cardiotoxicity associated with high dose cyclophosphamide therapy. *Arch Intern Med.* 1981;141(6):758–63.
13. Ando M, Yokozawa T, Sawada J, et al. Cardiac conduction abnormalities in patients with breast cancer undergoing high-dose chemotherapy and stem cell transplantation. *Bone Marrow Transplant.* 2000;25(2):185–9.
14. Curigliano G, Mayer EL, Burstein HJ,et al. Cardiac toxicity from systemic cancer therapy: a comprehensive review. *Prog Cardiovasc Dis.* 2010;53(1):94–104.

15. Morandi P, Ruffini PA, Benvenuto GM, et al. Cardiac toxicity of high-dose chemotherapy. *Bone Marrow Transplant*. 2005;35(4):323–34.
16. Cil T, Kaplan MA, Altintas A, et al. Cytosinearabinoside induced bradycardia in patient with non-Hodgkin lymphoma: a case report. *Leuk Lymphoma*. 2007;48(6):1247–9.
17. Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med.* 1993;118(1):31–6.
18. Olivieri A, Corvatta L, Montanari M, et al. Paroxysmal atrial fibrillation after high-dose melphalan in five patients autotransplanted with blood progenitor cells. *Bone Marrow Transplant.* 1998;21(10):1049–53.
19. Moreau P, Milpied N, Mahe´ B, Juge-Morineau N, et al. Melphalan 220 mg/m2 followed by peripheral blood stem cell transplantation in 27 patients with advanced multiple myeloma. *Bone Marrow Transplant.* 1999;23(10): 1003–6.
20. Phillips GL, Meisenberg B, Reece DE, et al. Amifostine and autologous hematopoietic stem cell support of escalating-dose melphalan: a phase I study. *Biol Blood Marrow Transplant.* 2004;10(7):473–83.
21. Feliz V, Saiyad S, Ramarao SM, et al. Melphalan-induced supraventricular tachycardia: incidence and risk factors. *Clin Cardiol.* 2011;34(6):356–9.
22. Floyd JD, Nguyen DT, Lobins RL, et al. Cardiotoxicity of cancer therapy. *J Clin Oncol*. 2005; 23(30):7685–96.
23. Guglin M, Aljayeh M, Saiyad S, et al. Introducing a new entity: chemotherapy-induced arrhythmia. *Europace.* 2009;11(12):1579–86.
24. Tomkowski WZ, Wis´niewska J, Szturmowicz M, et al. Evaluation of intrapericardial cisplatin administration in cases with recurrent malignant pericardial effusion and cardiac tamponade. *Support Care Cancer.* 2004;12(1):53–7.
25. Bischiniotis TS, Lafaras CT, Platogiannis DN, et al. Intrapericardial cisplatin administration after pericardiocentesis in patients with lung adenocarcinoma and malignant cardiac tamponade. *Hellenic J Cardiol*. 2005;46(5):324–9.
26. Richards WG, Zellos L, Bueno R, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. *J Clin Oncol*. 2006;24(10):1561–7.
27. Tamargo J, Caballero R, Delpo´n E. Drug-induced atrial fibrillation. *Expert Opin Drug Saf*. 2012;11(4):615–34.
28. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol*. 1992;10(11):1795–801.
29. Hrovatin E, Viel E, Lestuzzi C, et al. Severe ventricular dysrhythmias and silent ischemia during infusion of the antimetabolite 5-fluorouracil and cis-platin. *J Cardiovasc Med (Hagerstown).* 2006;7(8):637–40.
30. Polk A, Vaage-Nilsen M, Vistisen K, et al. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treat Rev.* 2013;39(8):974–84.
31. Khan MA, Masood N, Husain N, et al. A retrospective study of cardiotoxicities induced by 5-fluouracil (5-FU) and 5-FU based chemotherapy regimens in Pakistani adult cancer patients at Shaukat Khanum Memorial Cancer Hospital and Research Center. *J Pak Med Assoc.* 2012;62(5): 430–4.
32. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf*. 2009;8(2): 191–202.
33. Keefe DL, Roistacher N, Pierri MK. Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol*. 1993;33(11):1060–70.
34. Yilmaz U, Oztop I, Ciloglu A, et al. 5-fluorouracil increases the number and complexity of prematüre complexes in the heart: a prospective study using ambulatory ECG monitoring. *Int J Clin Pract.* 2007;61(5): 795–801.
35. Eskilsson J, Albertsson M. Failure of preventing 5-fluorouracil cardiotoxicity by prophylactic treatment with verapamil. *Acta Oncol.* 1990;29(8):1001–3.
36. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol.* 2008;134(1):75–82.
37. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. *Cancer*. 1993;71(2):493–509.

38. Santini D, Tonini G, Abbate A, et al. Gemcitabine-induced atrial fibrillation: a hitherto unreported manifestation of drug toxicity. *Ann Oncol*. 2000;11(4):479–81.
39. Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. *Cancer Treat Rev.* 2011;37(4):300–11.
40. Alter P, Herzum M, Soufi M, et al. Cardiotoxicity of 5-fluorouracil. *Cardiovasc Hematol Agents Med Chem*. 2006;4(1):1–5.
41. Becker K, Erckenbrecht JF, Ha¨ussinger D, et al. Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs.* 1999;57(4):475–84.
42. McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med.* 1989;111(4):273–9.
43. Arbuck SG, Strauss H, Rowinsky E, et al. A reassessment of cardiac toxicity associated with taxol. *J Natl Cancer Inst Mono.* 1993;15:117–30.
44. Rowinsky EK, Eisenhauer EA, Chaudhry V, et al. Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol.* 1993;20(4 Suppl 3):1–15.
45. Bristow MR, Sageman WS, Scott RH, et al. Acute and chronic cardiovascular effects of doxorubicin in the dog: the cardiovascular pharmacology of drug-induced histamine release. *J Cardiovasc Pharmacol.* 1980;2(5):487–515.
46. Yancy RS, Talpaz M. Vindesine associated angina and ECG changes. *Cancer Treat Rep*. 1982;66(3):587–9.
47. Subar M, Muggia FM. Apparent myocardial ischemia associated with vinblastine administration. *Cancer Treat Rep*. 1986;70(5): 690–1.
48. Roca E, Bruera E, Politi PM, et al. Vinca alkaloid-induced cardiovascular autonomic neuropathy. *Cancer Treat Rep.* 1985;69(2):149–51.
49. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer.* 2010;10:337.
50. Dindogru A, Barcos M, Henderson ES, et al. Electrocardiographic changes following adriamycin treatment. *Med Pediatr Oncol*. 1978;5(1):65–71.
51. Schimmel KJ, Richel DJ, Van den Brink RB, et al. Cardiotoxicity of cytotoxic drugs. *Cancer Treat Rev*. 2004;30(2):181–91.
52. Kilickap S, Barista I, Akgul E, et al. Early and late arrhythmogenic effects of doxorubicin. *South Med J.* 2007;100(3):262–5.
53. O'Bryan RM, Luce JK, Talley RW, et al. Phase II evaluation of adriamycin in human neoplasia. *Cancer*. 1973;32(1):1–8.
54. Steinberg JS, Cohen AJ, Wasserman AG, et al. Acute arrhythmogenicity of doxorubicin administration. *Cancer.* 1987;60(6):1213–8.
55. Outomuro D, Grana DR, Azzato F, et al. Adriamycin-induced myocardial toxicity: new solutions for an old problem? *Int J Cardiol.* 2007;117(1):6–15.
56. Hayek ER, Speakman E, Rehmus E. Acute doxorubicin cardiotoxicity. *N Engl J Med*. 2005;352(23):2456–7.
57. Wortman JE, Lucas VS Jr, Schuster E, et al. Sudden death during doxorubicin administration. *Cancer.* 1979;44(5):1588–91.
58. Couch RD, Loh KK, Sugino J. Sudden cardiac death following adriamycin therapy. *Cancer.* 1981;48(1):38–9.
59. Rudzinski T, Ciesielczyk M, Religa W, et al. Doxorubicin-induced ventricular arrhythmia treated by implantation of an automatic cardioverter–defibrillator. *Europace.* 2007;9(5):278–80.
60. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions a scientific statement from the American Heart Association. *Circulation*. 2013;128(17):1927–95.
61. Steinherz LJ, Steinherz PG, Tan C. Cardiac failure and dysrhythmias 6–19 years after anthracycline therapy: a series of 15 patients. *Med Pediatr Oncol*. 1995;24(6):352–61.
62. Larsen RL, Jakacki RI, Vetter VL, et al. Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults. *Am J Cardiol.* 1992;70(1):73–7.
63. Altena R, Perik PJ, van Veldhuisen DJ, et al. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol.* 2009;10(4):391–9.

64. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc.* 2014;3(2):e000665.
65. Keung EC, Toll L, Ellis M, Jensen RA. L-type cardiac calcium channels in doxorubicin cardiomyopathy in rats: morphological, biochemical, and functional correlations. *J Clin Invest*. 1991;87(6):2108–13.
66. Huang SY, Chang CS, Tang JL, et al. Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. *Br J Haematol.* 1998;103(4):1092–5.
67. Ohnishi K, Yoshida H, Shigeno K, et al. Arsenic trioxide therapy for relapsed or refractory Japanese patients with acute promyelocytic leukemia: need for careful electrocardiogram monitoring. *Leukemia*. 2002;16(4): 617–22.
68. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. *J Clin Oncol.* 2003;21(19):3609–15.
69. Soignet SL, Frankel SR, Douer D, Tallman et al. United states multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol.* 2001;19(18):3852–60.
70. Beer TM, Tangen CM, Nichols CR, et al. Southwest Oncology Group phase II study of arsenic trioxide in patients with refractory germcell malignancies. *Cancer.* 2006;106(12):2624–9.
71. Westervelt P, Brown RA, Adkins DR, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood.* 2001;98(2): 266–71.
72. Unnikrishnan D, Dutcher JP, Garl S, et al. Cardiac monitoring of patients receiving arsenic trioxide therapy. *Br J Haematol*. 2004;124(5):610–7.
73. Drolet B, Simard C, Roden DM. Unusual effects of a QT-prolonging drug, arsenic trioxide, on cardiac potassium currents. Circulation. 2004;109(1):26–9.
74. Budd GT, Bukowski RM, Miketo L, et al. Phase I trial of ultrapure human leukocyte interferon in human malignancy. *Cancer Chemother Pharmacol.* 1984;12(1): 39–42.
75. Martino S, Ratanatharathorn V, Karanes C, et al. Reversible arrhythmias observed in patients treated with recombinant alpha 2 interferon. *J Cancer Res Clin Oncol.* 1987;113(4):376–8.
76. Fries GG, Brown TD, Wrenn RC. Cardiovascular rhythm effects of gamma recombinant DNA interferon. *Invest New Drugs*. 1989;7(2–3):275–80.
77. Sonnenblick M, Rosin A. Cardiotoxicity of interferon: a review of 44 cases. *Chest*. 1991;99(3):557–61.
78. Lee RE, Lotze MT, Skibber JM, et al. Cardiorespiratory effects of immunotherapy with interleukin-2. *J Clin Oncol.* 1989;7(1):7–20.
79. Bates SE, Rosing DR, Fojo T, et al. Challenges of evaluating the cardiac effects of anticancer agents. *Clin Cancer Res*. 2006;12(13):3871–4.
80. Full prescribing information for ZOLINZA_ (vorinostat) [package insert]. https://www.merck.com/product/usa/pi_circulars/z/zolinza/zolinza_pi.pdf. Accessed 1 Sep 2014.
81. Sandor V, Bakke S, Robey RW, et al. Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. *Clin Cancer Res*. 2002;8(3):718–28.
82. Piekarz RL, Frye AR, Wright JJ, et al. Cardiac studies in patients treated with depsipeptide, FK229, in a phase II trial for T-cell lymphoma. *Clin Cancer Res.* 2006;12(12):3762–73.
83. Shah MH, Binkley P, Chan K, Xiao J, et al. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. *Clin Cancer Res.*2006;12:3997–4003.
84. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25(21):3109–15.
85. Rowinsky E, Bono J, Deangelo D, et al. Cardiac monitoring in phase I trials of a novel histone deacetylase (HDAC) inhibitor LAQ825 in patients with advanced solid tumor and hematologic malignancies. *J Clin Oncol* 2005;23:3131
86. Orcioulo E, Buda G, Cecconi N, et al. Unexpected cardiotoxicity in haematological bertozomib treated patients. *Br J Haematol.* 2007;138(3): 396–403.
87. Xiao Y, Yin J, Wei J, et al. Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. *PLoS One*. 2014;9(1):e87671.
88. Barlogie B, Tricot G,Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354(10):1021–30.
89. Fahdi IE, Gaddam V, Saucedo JF, et al. Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol.* 2004;93(8):1052–5.

90. Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006;24(3):431–6.
91. Kaur A, Yu SS, Lee AJ, et al. Thalidomide-induced sinüs bradycardia. *Ann Pharmacother*. 2003;37:1040–3.
92. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. *Blood.* 2008;111(8):3968–77.
93. Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). *Blood.* 2005;105(7):2949–51.
94. Von Hoff DD, Elson D, Polk G, et al. Acute ventricular fibrillation and death during infusion of 40-(9-acridinylamino) methanesulfon-m-ansidide (AMSA). Cancer Treat Rep. 1980;64(2–3):356–8.
95. Louie AC, Issell BF. Amsacrine (AMSA)—a clinical review. *J Clin Oncol.* 1985;3(4):562–92.
96. Falkson G. Multiple ventricular extrasystoles following administration of 40-(9-aciridinylamino) methanesulfon-m-anisidide (AMSA). *Cancer Treat Rep.* 1980;64(2–3):358.
97. Steinherz LJ, Steinherz PG, Mangiacasale D, et al. Cardiac abnormalities after AMSA administration. *Cancer Treat Rep*. 1982;66(3):483–8.
98. Shinar E, Hasin Y. Acute electrocardiographic changes induced by amsacrine. *Cancer Treat Rep*. 1984;68(9):1169–72.
99. Fenaux P, Tertian G, Castaigne S, et al. A randomized trial of amsacrine and rubidazone in 39 patients with acute promyelocytic leukemia. *J Clin Oncol.* 1991;9(9):1556–61.
100. Weiss AJ, Manthel RW. Experience with the use of Adriamycin in combination with other anticancer agents using a weekly schedule with particular reference to lack of cardiac toxicity. *Cancer*. 1977;40(5):2046–52.
101. Thomas D, Hammerling BC, Wu K, et al. Inhibition of cardiac HERG currents by the DNA topoisomerase II inhibitor amsacrine: mode of action. *Br J Pharmacol.* 2004;142(3):485–94.
102. Mellor HR, Bell AR, Valentin JP, et al. Cardiotoxicity associated with targeting kinase pathways in cancer. *Toxicol Sci.* 2011;120(1):14–32.
103. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT Interval). *Drug Saf.* 2013;36(5):295–316.
104. Petrini I, Lencioni M, Ricasoli M, et al. Phase II trial of sorafenib in combination with 5-fluorouracil infusion in advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol*. 2012;69(3):773–80.
105. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet*. 2007;370(9604):2011–9.
106. Bello CL, Mulay M, Huang X, et al. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: pharmacokinetic-pharmacodynamic evaluation of sunitinib. *Clin Cancer Res.* 2009;15(22):7045–52.
107. Mego M, Reckova M, Obertova J, et al. Increased cardiotoxicity of sorafenib in sunitinibpretreated patients with metastatic renal cell carcinoma. *Ann Oncol.* 2007;18(11):1906–7.
108. Prescribing information for ICLUSIG_ (ponatinib) tablets for oral use. http://www.accessdata.fda.gov/drugsatfda_docs/label/ 2012/203469lbl.pdf. Accessed 1 Sep 2014.