Bölüm
37

GESTASYONEL MEME KANSERİNDE SİSTEMİK TEDAVİ

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GİRİŞ

Gebelikte meme kanseri oldukça nadir olmasına rağmen, gebelik sırasında oluşan kanser türleri arasında en sık ortaya çıkan kanserdir. 16-49 yaş arası meme kanseri tanısı konan hastaların 1000' de 4' ünü kapsamaktadır. Gebelikle ilgili meme kanseri teşhisi, kadınların çocuk doğurma yaşının yükselmesinden dolayı son yıllarda da artış göstermektedir (1,2). Kadının ilk gebeliğini 35 yaş veya daha sonraki yaşlara ertelemesi, meme kanseri olma riskini 20 yaşından önce gebe kalanlara göre üç kez arttırmaktadır (3). Gebelikle ilişkili meme kanseri ortalama tanı yaşı 32-34 arasındadır (4). Gebelikle ilişkili veya Gestasyonel meme kanseri terimi (GİMK), gebelik döneminde veya postpartum dönemde bir yıl içinde ya da laktasyonun herhangi bir zamanında oluşan meme kanserlerini kapsamaktadır. Meme kanseri olan gebe hastayı gebe olmayan meme kanseri hastası kadar etkili bir şekilde tedavi etme arzusuna rağmen, hem annenin hem de fetüsün güvenliğini sağlamak için standart tedavilerin seçimi ve sunulması modifiye edilmelidir. Gebelikte meme kanserinin tanı, tedavisi ve sonuçları hakkında prospektif çalışma çok azdır; klinik kanıtların çoğu retrospektif vaka serileri ve vaka raporlarından oluşmaktadır.

TEDAVİ

GİMK vakalarında histopatolojik olarak en çok karşılaşılan tip, gebe olmayanlarda da olduğu gibi, invaziv duktal karsinom tipidir. Literatürde çelişkili sonuçlar olmakla birlikte bazı analizlerde, gebelikte meme dokusunda görülen fizyolojik değişikliklerin tanıda çoğu zaman gecikmeye neden olmasıyla da ilgili olarak,

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SONUÇ

Gebelikle ilişkili meme kanseri tanısı göreceli olarak nadir bir klinik durumdur. Tedavisi hasta, kadın doğum uzmanı, tıbbi onkolog, cerrahi ve radyasyon onkoloğunu içeren multidisipliner bir yaklaşımla yapılmalıdır. Standart tedaviler ile ilgili güvenlik ve etkinlik verileri giderek artmaktadır. Bu nedenle gebe meme kanserinde optimal kanser kontrolü için minimal gecikme ile başlanmalıdır. Fetüsün güvenliği de sağlanarak, hamile olmayan hastalar için uygulanan standart protokollere gebe hastalarda da mümkün olduğunca bağlı kalınmalıdır. Tedavi şekli hastalığın evresine, tümör biyolojisine, doğumda gebelik yaşına, muhtemel materno-fetal risklerine ve hastanın isteğine göre şekillendirilmelidir.

Kemoterapi 12. gebelik haftasından önce ve 34-35. gebelik haftalarından sonra yapılmamalıdır. Antrasiklin bazlı rejimler erken ve ileri evre hastalıkta tercih edilebilir. Bilgiler sınırlı olmakla beraber tek ajan haftalık taksan uygulaması da hem neoadjuvan, adjuvan, metastatik hastalıkta ve hem de antrasiklin alamayacak hastalarda alternatif olarak kullanılabilir. Trastuzumab ile ilgili de sınırlı veri nedeniyle hamilelik süresince bu ilaç kullanımından mümkün olduğunca kaçınılmalıdır. Eğer kullanma gerekliliği varsa, sadece bir trimester ile sınırlı olmalı ve amniyotik sıvı hacmi yakın izleme alınmalıdır**.** Endokrin tedavi doğum sonrasına ertelenmelidir. Prematürite ile ilişkili fetal morbidite riskini azaltmak için en az 35-37 gebelik haftasına kadar doğumun geciktirilmesi için çaba gösterilmelidir. İntrauterin kemoterapiye maruz kalmış çocukların değerlendirilmeleri ve uzun süreli takibi gerekmektedir.

Kemoterapi, trastuzumab, lapatinib ve endokrin tedavisi alan kadınlarda emzirmekten kaçınılmalıdır. Bununla birlikte, meme kanseri için tedavi tamamlandıktan sonra emzirme, özellikle kontralateral göğüste ve laktasyon danışmanlığı ile güvenli ve uygulanabilir görünmektedir.

Anahtar Kelimeler: Meme kanseri, gebelik, sistemik tedavi.

KAYNAKLAR

1. Litton JK, Theriault RL, Gonzalez-Angulo AM. Breast cancer diagnosis during pregnancy. Womens Health (Lond Engl). 2009;5:243-249. (PMID: 19392610)
2. Stensheim H, Moller B, van Dijk T, et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol.2009;27:45-51.
3. Kulshrestha M. Pregnancy-associated breast cancer. J S Asian Fed Obstet Gynecol. 2011; 3:1-5.
4. Mathelin C, Annane K, Treisser A et al. Pregnancy and Post-partum Breast Cancer: A Prospective Study. Anticancer Res. 2008;28:2447-2452.
5. Ishida T, Yokoe T, Kasumi F, et al. Clinicopathologic characteristics and prognosis of breast cancer patients associated with pregnancy and lactation:analysis of case-control study in Japan. Jpn J Cancer Res.1992; 83:1143-1149.

6. Halaska MJ, Pentheroudakis G, Strnad P, et al. Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: a matched controlled study. Breast J. 2009;15:461-7.
7. Gianopoulos JG. Establishing the criteria for anesthesia and other precautions for surgery during pregnancy. Surg Clin North Am.1995;75:33.
8. Mazze RI, Källén B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol.1989;161:1178.
9. Kuerer HM, Cunningham JD, Brower ST, et al. Breast carcinoma associated with pregnancy and lactation. Surg Oncol. 1997;6:93-98.
10. Gwyn K, Theriault R. Breast cancer during pregnancy. Oncology (Williston Park). 2001;15:39-46.
11. Keleher A, Wendt R, Delpassand E, et al. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. Breast J.2004;10:492-495.
12. Ring AE, Smith IE, Jones A, et al. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol.2005;23:4192-4197.
13. Greskovich JF, Jr, Macklis RM. Radiation therapy in pregnancy: risk calculation and risk minimization. Semin Oncol.2000;27:633-645.
14. FDA. Pregnancy Risk Categories. Food and Drug Administration. Federal Register. 1980;44:37434-37467.
15. Nugent P, O'Connell TX. Breast cancer and pregnancy. Arch Surg. 1985;120:1221-1224.
16. Tewari KS. Cancer in pregnancy, In: DiSaia PJ, Cresman WT (Eds). Clinical Gynecologic Oncology, 8th ed. Philedelphia, Saunders-Elsevier. 2012, pp 405-478.
17. Zemlickis D, Lishner M, Degendorfer P, et al. Maternal and fetal outcome after breast cancer in pregnancy. Am J Obstet Gynecol.1992;166:781-787.
18. Giacalone PL, Laffargue F, Bénos P. Chemotherapy for breast carcinoma during pregnancy: A French national survey. Cancer. 1999; 86:2266.
19. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004; 5:283.
20. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol. 1999;17:855-861.
21. Murthy RK, Theriault RL, Barnett CM, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. Breast Cancer Res.2014; 16:500.
22. rmann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. Ann Oncol.2004;15:146-150.
23. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study**.** Lancet Oncol. 2012;13(9):887-896. doi: 10.1016/S1470-2045(12)70261-9.
24. Peres RM, Sanseverino MT, Guimarães JL, et al. Assessment of fetal risk associated with exposure to cancer chemotherapy during pregnancy: a multicenter study. Braz J Med Biol Res. 2001; 34:1551.
25. Achtari C, Hohlfeld P. Cardiotoxic transplacental effect of idarubicin administered during the second trimester of pregnancy. Am J Obstet Gynecol.2000;183:511.
26. Kelly HL, Collichio FA, Dees EC. Concomitant pregnancy and breast cancer: options for systemic therapy. Breast Dis.2006;23:95-101.
27. Gziri MM, Debièvе F, DE Catte L, et al. Chemotherapy during pregnancy: effect of anthracyclines on fetal and maternal cardiac function. Acta Obstet Gynecol Scand. 2012; 91:1465.
28. Murray CL, Reichert JA, Anderson J, et al. Multimodal cancer therapy for breast cancer in the first trimester of pregnancy. A case report. JAMA. 1984;252(18):2607-2608.
29. Zemlickis D, Lishner M, Erlich R. et al. Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide. Teratog Carcinog Mutagen.1993;13(3):139-143.
30. Zemlickis D, Klein J, Moselhy G et al. Cisplatin protein binding in pregnancy and the neonatal period. Med Pediatr Oncol.1994;23(6):476.
31. Mir O, Berveiller P, Ropert S, et al. Use of platinum derivatives during pregnancy. Cancer. 2008;113(11):3069-3074. doi: 10.1002/cncr.23935.

32. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxans for breast cancer during pregnancy: a systematic review. Clin Breast Cancer. 2013;13(1):16-23.
33 .Mir O, Berveiller P, Goffinet F, et al. Taxanes for breast cancer during pregnancy: a systematic review. Ann Oncol. 2010;21(2):425.
34. Cuvier C, Espie M, Extra JM, et al. Vinorelbine in pregnancy. Eur J Cancer. 1997;33:168-169.
35. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer. 107 (2006), pp. 1219-1226.
36. Cardonick E, Usmani A, Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. Am J Clin Oncol. 2010;33(3):221-228. doi: 10.1097/COC.0b013e3181a44ca9.
37. H. Azim, H.A. Azim Jr. Targeting Her-2/neu in breast cancer: as easy as this! Oncology. 74 (2008), pp. 150-157.
38. ERCEPTIN®(trastuzumab)PrescribingInformationhttp://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5256lbl.pdf
39. Zagouri F, Sergentanis TN, Chrysikos D, et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. Breast Cancer Res Treat.2013;137:349.
40. N. Pentsuk, J.W. van der Laan. An interspecies comparison of placental antibody transfer: new insights into development toxicity testing of monoclonal antibodies. Birth Defects Res B Dev Reprod Toxicol. 86 (2009), pp. 328-344.
41. Azim Jr HA, Azim H, Peccatori FA. Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge. Expert Rev Clin Immunol.2010;6:821e6.
42. Gottschalk I, Berg C, Harbeck N, et al. Fetal Renal Insufficiency Following Trastuzumab Treatment for Breast Cancer in Pregnancy: Case Report und Review of the Current Literature. Breast Care (Basel). 2011;6(6):475-478.
43. Azim HA Jr, Metzger-Filho O, de Azambuja E, et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). Breast Cancer Res Treat. 2012; 133:387-391.
44. Yildirim N, Bahceci A. Use of pertuzumab and trastuzumab during pregnancy. Anti-Cancer Drugs. 2018;29:810-813. DOI: 10.1097/CAD.0000000000000658
45. Kelly H, Graham M, Humes E, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. Clin Breast Cancer. 2006;7(4): 339-341.
46. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. JAMA. 1994;271(24):1905.
47. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy--case report and literature review. Gynecol Oncol. 2001;80(3):405.
48. Tewari K, Bonebrake RG, Asrat T et al. Ambiguous genitalia in infant exposed to tamoxifen in utero. Lancet.1997;350:183.
49. Loibl S, Schmidt A, Gentilini O et al. Breast cancer diagnosed during pregnancy: Adapting recent advances in breast cancer care for pregnant patients. JAMA Oncol. 2015;1:1145-1153.
50. Kytril (Granisetron HCl). Nutley, NRL, Inc., NJ: Roche, September 2009.
51. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med.2013;368:814-823.
52. Einarson A, Maltepe C, Navioz Y et al. The safety of ondansetron for nausea and vomiting of pregnancy: A prospective comparative study. BJOG. 2004;111:940-943.
53. US Food and Drug Administration. FDA drug safety communication: Abnormal heart rhythms may be associated with use of Zofran (ondansetron). Accessed May 1, 2016.
54. Koren G. Motherisk update. Is ondansetron safe for use during pregnancy? Can Fam Physician. 2012;58:1092-1093.
55. Ondansetron. Ondansetron Prescribing Information. Revised 11/2012. Accessed May 1, 2016.
56. Emend (Aprepitant) [package insert]. Whitehouse Station, NJ: Merck, December 2015. Accessed May 1, 2016.

57. Crowther CA, Doyle LW, Haslam RR, et al. ACTORDS Study Group. Outcomes at 2 Years of Age after Repeat Doses of Antenatal Corticosteroids. N Engl J Med. 2007;357:1179-1189 DOI: 10.1056 /NEJMoa071152.
58. Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. Am J Obstet Gynecol. 1977;127:264-267.
59. Gilboa SM, Ailes EC, Rai RP et al. Antihistamines and birth defects: A systematic review of the literature. Expert Opin Drug Saf. 2014;13:1667-1698.
60. Schatz M, Petitti D. Antihistamines and pregnancy. Ann Allergy Asthma Immunol 1997;78:157-159.
61. Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. Obstet Gynecol. 2012;120:1267-1272.
62. Cardonick E, Irfan F, Torres N. The use of Neupogen (filgrastim) or Neulasta (pegfilgrastim) during pregnancy when chemotherapy is indicated for maternal cancer treatment. J Cancer Ther.2012;3:5.
63. Bilgin K, Yaramiş A, Haspolat K, et al. A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. Pediatrics. 2001;107:36.
64. Schibler KR, Osborne KA, Leung LY, et al. A randomized, placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. Pediatrics.1998;102:6.
65. Helewa M, Levesque P, Provencher D, et al. Breastcancer, pregnancyandbreastfeeding. J Obstet-Gynaecol Can. 2002;24:164-180.(PMID: 12196882).
66. N Pavlidis, G Pentheroudakis. Metastatic involvement of placenta and foetus in pregnant women with cancer. Recent Results Cancer Res.178 (2008), pp. 183-194.
67. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation, 8th ed, Lippincott Williams & Wilkins, Philadelphia, PA 2008.
68. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. J Natl Med Assoc. 1979; 71:165.
69. N Pavlidis, G Pentheroudakis. The pregnant mother with breast cancer: diagnostic and therapeutic management. Cancer Treat Rev. 31 (2005), pp. 439-447.
70. JA Petrek, R Dukoff, A Rogatko. Prognosis of pregnancy-associated breast cancer. Cancer, 67 (1991), pp. 869-872.
71. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013;31(20):2532. Epub 2013 Apr 22.
72. Azim HA Jr, Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. Cancer Treat Rev. 2012; 38:834.
73. J.K. Litton, C.L. Warneke, K.M. Hahn, et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. Oncologist. 18 (2013), pp. 369-376
74. Ploquin A, Pistilli B, Tresch E, et al. 5-year overall survival after early breast cancer diagnosed during pregnancy: A retrospective case-control multicentre French study. Eur J Cancer. 2018;95:30-37. doi: 10.1016/j.ejca.2018.02.030.
75. E.K. Hartman, G.D. Eslick. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 160 (2016), pp. 347-360.
76. Litton JK and Theriault RL. Breast cancer and pregnancy: current concepts in diagnosis and treatment. Oncologist.2010;15(12):1238-1247.
77. Deemarsky L, Neishtadt E. Breast cancer and pregnancy. Breast. 1981;7:17.
78. Clark RM, Chua T. Breast cancer and pregnancy: The ultimate challenge. Clin Oncol (R Coll Radiol) 1989;1:11-18.
79. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer.2006;107:1219-1226.

80. Cardonick E, Dougherty R, Grana G, et al. Breast cancer during pregnancy: Maternal and fetal outcomes. Cancer J. 2010;16:76-82.
81. Queisser-Luft A, Stolz G, Wiesel A, et al. Malformations in newborn: Results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990–1998) Arch Gynecol Obstet. 2002;266:163-167.
82. Amant F, Vandenbroucke T, Verheecke M, et al. Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. N Engl J Med. 2015;373(19):1824.
83. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018;19(3):337.