Bölüm
26

METASTATİK OSTEOSARKOMDA SİSTEMİK TEDAVİ

Hayriye ŞAHİNLİ[1]

GİRİŞ

Osteosarkom çocuk ve adelosanlarda görülen en yaygın primer kemik tümörlerinden birisidir. Her yıl 0-24 yaş aralığındaki 1 milyon bireyde 4,4 yeni vaka çıktığı tahmin edilmektedir. Ortalama görülme yaşı 20 yıldır. Sekonder osteosarkomun ise ortalama görülme yaşı 65 tir. Osteosarkom hematojen yolla yayılır ve en sık metastaz yaptığı organ akciğerdir. Etkili bir kemoterapi ile osteosarkomlu hastaların sağkalım süreleri dramatik bir şekilde artmıştır. Sistemik kemoterapinin kullanımından önce tümörün lokal kontrolüne rağmen hastaların %80-90'nında metastaz gelişmekteydi ve metastazdan dolayı hastalar kaybedilmekteydi. Lokal tümör kontrolü sonrası kemoterapisiz sağkalım %16'larda idi. Tümörün rezeksiyonu ve mikrometastatik hastalığın kontrolü için verilen sistemik kemoterapi kombinasyonu osteosarkomun standart tedavisidir. Metastaz yapmamış, cerrahi olarak tüm lezyonu çıkarılmış hastalarda üçlü veya dörtlü sistemik kemoterapi kombinasyonları ile 5 yıllık sağkalım oranları %70'lere ulaşmıştır.

Primer metastatik osteosarkomlu hastalarda sistemik tedavi

Tanı anında hastaların %10-20'si metastatik hastalıkla prezente olmaktadır (1). Primer metastatik osteosarkomlu hastalarda prognoz kötüdür. Uzun dönem sağkalım standart kemoterapi ve cerrahi ile %10-50 arasındadır (2). Metastatik osteosarkomlu hastalarda, tümör alanlarının yaygın eksizyonu ve sistemik kemoterapi önerilmektedir. Sistemik tedavi ve cerrahiyle kür elde edilebilmektedir. Metastazın sayı ve lokalizasyonunun prognostik önemi vardır. Yalnızca pulmoner metastazı olan hastalarda hastalıksız sağkalım %20-30'larda olmaktadır. Tek taraflı metastaz ve az sayıda akciğer nodülü olan hastalarda sağkalım daha iyidir (3, 4). Sınırlı pulmoner metastazı olan hastaların %30-40'ı multimodal tedavi ile kür olabilmektedirler.

Tablo 1. NCCN kılavuzuna göre sistemik tedavi ajanları
Birinci basamak tedavi(primer/neoadjuvan/adjuvan veya metastatik hastalık)
Cisplatin ve doksurabisin (23-25)
MAP(yüksek doz metotreksat, cisplatin ve doksurabisin) (25-28)
Doksurabisin,cisplatin,ifosfamid ve yüksek doz metotreksat (10)
İfosfamid, cisplatin, ve epirubisin (29)
İkinci basamak tedavi(relaps/refraktör veya metastatik hastalık)
Dosataksel/gemsitabin (30)
Siklofosfamid/etoposid (14)
Siklofosfamid/topotekan (31)
Gemsitabin 49
İfosfamid(yüksek doz)±etoposid (11, 32)
İfosfamid,karboplatin ve etoposid (33)
Yüksek doz metotreksat,etoposid,ifosfamid (34)
Sm-EDTMP (relaps/refraktör hastalıkta 2.basamak tedavi) (35)
Ra 223 (19, 20)
Sorafenib (21)

SONUÇ

Metastatik osteosarkomlu hastaların prognozu kötü seyretmektedir. Tanı anında metastatik olup cerrahiye uygun olmayan hastalarda tek bir standart tedavi yaklaşımı yoktur. Primer metastatik osteosarkomlu hastalara öncelikle küratif amaçlı yaklaşılmalıdır. Rezektabl metastazlı hastalar için preoperatif tedavinin ardından yaygın eksizyon ve metastazektomi önerilmektedir.

Relaps veya refraktör hastalar için ise 2.sıra kemoterapi ve mümkünse yeniden rezeksiyon önerilir.

KAYNAKLAR

1. Kager L, Zoubek A, Potschger U, Kastner U, Flege S, Kempf-Bielack B, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol. 2003;21(10):2011-8.
2. Aljubran AH, Griffin A, Pintilie M, Blackstein M. Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases. Ann Oncol. 2009;20(6):1136-41.
3. Bacci G, Briccoli A, Ferrari S, Saeter G, Donati D, Longhi A, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with synchronous lung metastases: treatment with cisplatin, adriamycin and high dose of methotrexate and ifosfamide. Oncol Rep. 2000;7(2):339-46.
4. Daw NC, Billups CA, Rodriguez-Galindo C, McCarville MB, Rao BN, Cain AM, et al. Metastatic osteosarcoma. Cancer. 2006;106(2):403-12.

5. Winkler K, Torggler S, Beron G, Bode U, Gerein V, Jurgens H, et al. [Results of treatment in primary disseminated osteosarcoma. Analysis of the follow-up of patients in the cooperative osteosarcoma studies COSS-80 and COSS-82]. Onkologie. 1989;12(2):92-6.
6. Ferguson WS, Harris MB, Goorin AM, Gebhardt MC, Link MP, Shochat SJ, et al. Presurgical window of carboplatin and surgery and multidrug chemotherapy for the treatment of newly diagnosed metastatic or unresectable osteosarcoma: Pediatric Oncology Group Trial. J Pediatr Hematol Oncol. 2001;23(6):340-8.
7. Meyers PA, Heller G, Healey JH, Huvos A, Applewhite A, Sun M, et al. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. J Clin Oncol. 1993;11(3):449-53.
8. Harris MB, Gieser P, Goorin AM, Ayala A, Shochat SJ, Ferguson WS, et al. Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group Study. J Clin Oncol. 1998;16(11):3641-8.
9. Edmonson JH, Creagan ET, Gilchrist GS. Phase II study of high-dose methotrexate in patients with unresectable metastatic osteosarcoma. Cancer Treat Rep. 1981;65(5-6):538-9.
10. Bacci G, Briccoli A, Rocca M, Ferrari S, Donati D, Longhi A, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. Ann Oncol. 2003;14(7):1126-34.
11. Goorin AM, Harris MB, Bernstein M, Ferguson W, Devidas M, Siegal GP, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. J Clin Oncol. 2002;20(2):426-33.
12. Heymann MF, Brown HK, Heymann D. Drugs in early clinical development for the treatment of osteosarcoma. Expert Opin Investig Drugs. 2016;25(11):1265-80.
13. Gentet JC, Brunat-Mentigny M, Demaille MC, Pein F, Avet-Loiseau H, Berger C, et al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. Eur J Cancer. 1997;33(2):232-7.
14. Berger M, Grignani G, Ferrari S, Biasin E, Brach del Prever A, Aliberti S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. Cancer. 2009;115(13):2980-7.
15. Qi WX, He AN, Tang LN, Shen Z, Lin F, Yao Y. Efficacy and safety of gemcitabine-docetaxel combination therapy for recurrent or refractory high-grade osteosarcoma in China: a retrospective study of 18 patients. Jpn J Clin Oncol. 2012;42(5):427-31.
16. Mora J, Cruz CO, Parareda A, de Torres C. Treatment of relapsed/refractory pediatric sarcomas with gemcitabine and docetaxel. J Pediatr Hematol Oncol. 2009;31(10):723-9.
17. Song BS, Seo J, Kim DH, Lim JS, Yoo JY, Lee JA. Gemcitabine and docetaxel for the treatment of children and adolescents with recurrent or refractory osteosarcoma: Korea Cancer Center Hospital experience. Pediatr Blood Cancer. 2014;61(8):1376-81.
18. Loeb DM, Garrett-Mayer E, Hobbs RF, Prideaux AR, Sgouros G, Shokek O, et al. Dose-finding study of 153Sm-EDTMP in patients with poor-prognosis osteosarcoma. Cancer. 2009;115(11):2514-22.
19. Subbiah V, Anderson P, Rohren E. Alpha Emitter Radium 223 in High-Risk Osteosarcoma: First Clinical Evidence of Response and Blood-Brain Barrier Penetration. JAMA Oncol. 2015;1(2):253-5.
20. Anderson PM, Subbiah V, Rohren E. Bone-seeking radiopharmaceuticals as targeted agents of osteosarcoma: samarium-153-EDTMP and radium-223. Adv Exp Med Biol. 2014;804:291-304.
21. Grignani G, Palmerini E, Dileo P, Asaftei SD, D'Ambrosio L, Pignochino Y, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. Ann Oncol. 2012;23(2):508-16.
22. Grignani G, Palmerini E, Ferraresi V, D'Ambrosio L, Bertulli R, Asaftei SD, et al. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. Lancet Oncol. 2015;16(1):98-107.
23. Bramwell VH, Burgers M, Sneath R, Souhami R, van Oosterom AT, Voute PA, et al. A compari-

son of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncol. 1992;10(10):1579-91.
24. Lewis IJ, Nooij MA, Whelan J, Sydes MR, Grimer R, Hogendoorn PC, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst. 2007;99(2):112-28.
25. Souhami RL, Craft AW, Van der Eijken JW, Nooij M, Spooner D, Bramwell VH, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet. 1997;350(9082):911-7.
26. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol. 2000;18(24):4016-27.
27. Winkler K, Beron G, Delling G, Heise U, Kabisch H, Purfurst C, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol. 1988;6(2):329-37.
28. Marina NM, Smeland S, Bielack SS, Bernstein M, Jovic G, Krailo MD, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. Lancet Oncol. 2016;17(10):1396-408.
29. Basaran M, Bavbek ES, Saglam S, Eralp L, Sakar B, Atalar AC, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. Oncology. 2007;72(3-4):255-60.
30. Navid F, Willert JR, McCarville MB, Furman W, Watkins A, Roberts W, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer. 2008;113(2):419-25.
31. Saylors RL, 3rd, Stine KC, Sullivan J, Kepner JL, Wall DA, Bernstein ML, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol. 2001;19(15):3463-9.
32. Miser JS, Kinsella TJ, Triche TJ, Tsokos M, Jarosinski P, Forquer R, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. J Clin Oncol. 1987;5(8):1191-8.
33. Van Winkle P, Angiolillo A, Krailo M, Cheung YK, Anderson B, Davenport V, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer. 2005;44(4):338-47.
34. Le Deley MC, Guinebretiere JM, Gentet JC, Pacquement H, Pichon F, Marec-Berard P, et al. SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. Eur J Cancer. 2007;43(4):752-61.
35. Anderson PM, Wiseman GA, Dispenzieri A, Arndt CA, Hartmann LC, Smithson WA, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol. 2002;20(1):189-96.