

## Bölüm 18

# UTERİN SARKOMLARDA SİSTEMİK TEDAVİ

Elif MEREV<sup>1</sup>

### GİRİŞ

Uterin sarkomlar malign mezankimal tümörlerdir. Uterus malignitelerinin %3–9'unu oluştururlar. Yıllık insidansı 0.36/100.000 kadın-yıldır.<sup>1</sup> Sık görülen alt tipleri endometriyal stromal sarkom (ESS, %21), uterin leiomyosarkom (uLMS, %63) ve andiferansiye uterin sarkomdur (UUS, %5).<sup>2,3</sup>

Endometriyal stromal sarkomlar düşük dereceli ve yüksek dereceli olmak üzere ikiye ayrılırlar. Düşük dereceli endometriyal stromal sarkomlar (LGESS) histolojik olarak; düşük dereceli küçük ve proliferatif endometriyumdaki stromal hücrelere benzeyen hücrelerden oluşurlar. Mitotik aktiviteleri genellikle düşüktür (<10/10 BBA). Yüksek dereceli endometriyal stromal sarkomlar (HGESS) histolojik olarak; yüksek dereceli küçük, sıklıkla nekroz içeren ve artmış mitotik aktivite (>10/10 BBA) hücrelerden oluşurlar, içlerinde LGESS alanları bulundurulabilirler. Andiferansiye uterin sarkomlar, histolojik olarak yüksek dereceli, stromal hücrelere bezemeyen ve spesifik farklılaşma göstermeyen hücrelerden oluşurlar. Uterin sarkomların takibi ve tedavisi, boyut (5 cm'in üstü ve altı), mitotik aktivite (10/BBA'da 10'un üstü ve altı), yaş (50 yaş üstü ve altı) ve vasküler invazyonun bulunup bulunmaması gibi klinikopatolojik faktörlere göre şekillenir.<sup>2</sup>

Düşük dereceli endometriyal stromal sarkomlar genellikle 40 ve 55 yaş arası premenapozal kadınlarda görülür. Tipik olarak hormon reseptörleri pozitif tümörlerdir.<sup>4</sup> Prognozları iyidir. Rekürrensler hastaların 3'te 1'inde gelişir ve yıllar sonra görülebilir. Beş yıllık sağkalımlar evre 1-2 için %90, evre 3-4 için %50'dir.<sup>5</sup> SEER (Surveillance Epidemiology and End Results) veritabanına göre düşük dereceli ve yüksek dereceli ESS'lerde tüm evreler için 5 yıllık rölatif sağkalım %72.7'dir.<sup>6</sup>

<sup>1</sup> Uzm. Dr., Karadeniz Teknik Üniversitesi Tıp Fakültesi Farabi Hastanesi Tıbbi Onkoloji Bilim Dalı, Trabzon, merevelif@gmail.com

vaad eden sonuçlar beklenmekteyse de henüz standart olarak kullanıma giren yoktur.<sup>61</sup>

**Anahtar Kelimeler:** Uterin sarkom, hormonal tedavi, kemoterapi

## KAYNAKLAR

1. Koivisto-Korander R., Martinsen J.I., Weiderpass E., Leminen A., Pukkala E. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. *Maturitas* 72 (2012), 56–60.
2. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of the Female Reproductive Organs, Volume 6, 2014.
3. Trope C.G., Abeler V.M., Kristensen G.B. Diagnosis and treatment of sarcoma of the uterus. A review. *Acta Oncol.* 51 (2012), 694–705.
4. Prat J, Mbatani 2015. Uterine sarcomas. *Int. J. Gynaecol. Obstet.* 131 (Suppl. 2), S105–S110.
5. Chan J.K., Kawar N.M., Shin J.Y., Osann K., Chen L.M., Powell C.B. et al. Endometrial stromal sarcoma: a population-based analysis. *Br. J. Cancer* 99 (2008), 1210–1215.
6. Hosh M., Antar S., Nazzal A., Warda M., Gibreel A., Refky B. Uterine sarcoma: analysis of 13,089 cases based on surveillance, epidemiology, and end results database. *Int. J. Gynecol. Cancer* 26 (2016), 1098–1104.
7. Abeler V.M., Roynø O., Thoresen S., Danielsen H.E., Nesland J.M., Kristensen G.B. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology* 54 (2009), 355–364.
8. Rauh-Hain JA, del Carmen MG. Endometrial stromal sarcoma: a systematic review. *Obstet Gynecol* 2013;122:676–683. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23921879>.
9. U.S. Department of Health and Human Services. FDA discourages use of laparoscopic power morcellation for removal of uterus or uterine fibroids Food and Drug Administration; 2014. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm393689.htm>. Accessed September 30, 2014
10. Bogani G, Cliby WA, Aletti GD. Impact of morcellation on survival outcomes of patients with unexpected uterine leiomyosarcoma: a systematic review and meta-analysis. *Gynecol Oncol* 2015;137:167–172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25462199>.
11. Corpus Uteri. In: AJCC Cancer Staging Manual, 7th, Edge SB, Byrd DR, Compton CC, et al (Eds), Springer, New York 2010. p.403.
12. Group EESNW. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23 Suppl 7:vii92-99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22997462>.
13. Shah JP, Bryant CS, Kumar S, et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. *Obstet Gynecol* 2008;112:1102-1108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18978112>.
14. Signorelli M, Fruscio R, Dell'Anna T, et al. Lymphadenectomy in uterine low-grade endometrial stromal sarcoma: an analysis of 19 cases and a literature review. *Int J Gynecol Cancer* 2010;20:1363-1366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21051978>.
15. Yamaguchi M, Erdenebaatar C, Saito F, Motohara T, Miyahara Y, Tashiro H, Katabuchi H. Long-Term Outcome of Aromatase Inhibitor Therapy With Letrozole in Patients With Advanced Low-Grade Endometrial Stromal Sarcoma. *Int J Gynecol Cancer.* 2015 Nov;25(9):1645-51.
16. Leath 3rd C.A., Huh W.K., Hyde Jr., J., Cohn D.E., Resnick K.E., Taylor N.P. et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. *Gynecol. Oncol.* 105 (2007), 630–634.
17. Zhou J. Et al. Influence of different treatment modalities on survival of patients with low-grade endometrial stromal sarcoma: a retrospective cohort study. *Int. J. Surg. (London, England)* 23 (Pt A), 147–151.

18. Malouf G.G., Duclos J., Rey A., Duvillard P., Lazar V., Haie-Meder C. et al. Impact of adjuvant treatment modalities on the management of patients with stages III endometrial stromal sarcoma. *Ann. Oncol.* 21 (2010), 2102–2106.
19. Amant F., De Knijf A., Van Calster B., Leunen K., Neven P., Berteloot P. et al. Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. *Br. J. Cancer* 97 (2007), 1194–1199.
20. Nadeem R, Catheryn M, Sarah B et al. Clinical Practice Guidelines in Oncology, Uterine Neoplasms Version 3.2019. [https://www.nccn.org/professionals/physician\\_gls/pdf/uterine.pdf](https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf)
21. Reich O, Regauer S. Estrogen replacement therapy and tamoxifen are contraindicated in patients with endometrial stromal sarcoma. *Gynecol Oncol* 2006;102:413-414; author reply 414. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16712906>. 380
22. Thanopoulou E, Judson I. Hormonal therapy in gynecological sarcomas. *Expert Rev Anticancer Ther* 2012;12:885-894. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22845404>.
23. Group EESNW. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23 Suppl 7:vii92-99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22997462>.
24. George S, Feng Y, Manola J, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. *Cancer* 2014;120:738-743. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24222211>.
25. Desar et al. Systemic treatment in adult uterine sarcomas. *Critical Reviews in Oncology/Hematology* Volume 122, February 2018, Pages 10-20.
26. Omura, G.A., Blessing, J.A., Major, F., Lifshitz, S., Ehrlich, C.E., Mangan, C., et al., 1985. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. *J. Clin. Oncol.* 3 (9), 1240–1245.
27. Hensley, M.L., Ishill, N., Soslow, R., Larkin, J., Abu-Rustum, N., Sabbatini, P., et al., 2009a. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: results of a prospective study. *Gynecol. Oncol.* 112 (3), 563–567.
28. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). *Cancer* 2013;119:1555-1561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23335221>.
29. Hempling, R.E., Piver, M.S., Baker, T.R., 1995. Impact on progression-free survival of adjuvant cyclophosphamide, vincristine, doxorubicin (adriamycin), and dacarbazine (CYVADIC) chemotherapy for stage I uterine sarcoma. A prospective trial. *Am. J. Clin. Oncol.* 18 (4), 282–286.
30. Amant F, Coosemans A, Debiec-Rychter M, et al. Clinical management of uterine sarcomas. *Lancet Oncol* 2009;10:1188-1198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19959075>.
31. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol* 2007;25:2755-2763. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17602081>.
32. Davis EJ, Chugh R, Zhao L, et al. A randomised, open-label, phase II study of neo/adjuvant doxorubicin and ifosfamide versus gemcitabine and docetaxel in patients with localised, high-risk, soft tissue sarcoma. *Eur J Cancer* 2015;51:1794-1802. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26066736>.
33. Hensley ML, Miller A, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol* 2015;33:1180- 1185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25713428>.
34. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002;20:2824-2831. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12065559>.
35. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft

- tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol* 2011;29:2528-2533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21606430>.
36. Mancari R, Signorelli M, Gadducci A, et al. Adjuvant chemotherapy in stage I-II uterine leiomyosarcoma: a multicentric retrospective study of 140 patients. *Gynecol Oncol* 2014;133:531-536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24631454>
  37. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PLETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879-1886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22595799>.
  38. Somaiah N, von Mehren M. New drugs and combinations for the treatment of soft-tissue sarcoma: a review. *Cancer Manag Res* 2012;4:397-411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23226072>.
  39. Rajendra R, Jones RL, Pollack SM. Targeted treatment for advanced soft tissue sarcoma: profile of pazopanib. *Onco Targets Ther* 2013;6:217-222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23524973>.
  40. Ferriss JS, Atkins KA, Lachance JA, et al. Temozolomide in advanced and recurrent uterine leiomyosarcoma and correlation with o6- methylguanine DNA methyltransferase expression: a case series. *Int J Gynecol Cancer* 2010;20:120-125. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20130512>
  41. Anderson S, Aghajanian C. Temozolomide in uterine leiomyosarcomas. *Gynecol Oncol* 2005;98:99-103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15916799>
  42. Gallup DG, Blessing JA, Andersen W, Morgan MA. Evaluation of paclitaxel in previously treated leiomyosarcoma of the uterus: a gynecologic oncology group study. *Gynecol Oncol* 2003;89:48-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12694653>.
  43. Chew I, Oliva E. Endometrial stromal sarcomas: a review of potential prognostic factors. *Adv Anat Pathol* 2010; 17:113.
  44. Thanopoulou E, Aleksic A, Thway K, Khabra K, Judson I. Hormonal treatments in metastatic endometrial stromal sarcomas: the 10-year experience of the sarcoma unit of Royal Marsden Hospital. *Clin Sarcoma Res.* 2015;5:8. Epub 2015 Mar 15.
  45. Tanner EJ, Garg K, Leitao MM Jr, Soslow RA, Hensley ML. High grade undifferentiated uterine sarcoma: surgery, treatment, and survival outcomes. *Gynecol Oncol.* 2012;127(1):27.
  46. Hemming ML, Wagner AJ, Nucci MR, Chiang S, Wang L, Hensley ML, George S. YWHAE-rearranged high-grade endometrial stromal sarcoma: Two-center case series and response to chemotherapy. *Gynecol Oncol.* 2017;145(3):531. Epub 2017 Apr 5.
  47. Karavasili V, Seddon BM, Ashley S, et al. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. *Cancer* 2008;112:1585-1591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18278813>.
  48. Leitao MM, Brennan MF, Hensley M, et al. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. *Gynecol Oncol* 2002;87:287-294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12468327>.
  49. Seagle, B.L., Sobocki-Rausch, J., Strohl, A.E., Shilpi, A., Grace, A., Shahabi, S., 2017. Prognosis and treatment of uterine leiomyosarcoma: a National Cancer Database study. *Gynecol. Oncol.* <http://dx.doi.org/10.1016/j.ygyno.2017.02.012>. pii: S00908258(17)30123-3
  50. Ray-Coquard, I., Rizzo, E., Blay, J.Y., Casali, P., Judson, I., Hansen, A.K., et al., 2016. Impact of chemotherapy in uterine sarcoma (UtS): review of 13 clinical trials from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) involving advanced/metastatic UtS compared to other soft tissue sarcoma (STS) patients treated with first line chemotherapy. *Gynecol. Oncol.* 142 (1), 95-101.
  51. Hensley, M.L., Blessing, J.A., Degeest, K., Abulafia, O., Rose, P.G., Homesley, H.D., 2008b. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol. Oncol.* 109 (3), 323-328.
  52. Long 3rd, H.J., Blessing, J.A., Sorosky, J., 2005. Phase II trial of dacarbazine, mitomycin, doxo-

- rubicin, and cisplatin with sargramostim in uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol. Oncol.* 99 (2), 339–342.
53. Pautier, P., Floquet, A., Penel, N., Piperno-Neumann, S., Isambert, N., Rey, A., et al., 2012. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). *Oncologist* 17 (9), 1213–1220.
  54. Seddon, B., Scurr, M., Jones, R.L., Wood, Z., Propert-Lewis, C., Fisher, C., et al., 2015. A phase II trial to assess the activity of gemcitabine and docetaxel as first line chemotherapy treatment in patients with unresectable leiomyosarcoma. *Clin. Sarcoma Res.* 5, 13.
  55. Seddon, B., Strauss, S.J., Whelan, J., Leahy, M., Woll, P.J., Cowie, F., et al., 2017. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol.* 18 (10), 1397–1410.
  56. Pautier, P., Floquet, A., Chevreau, C., Penel, N., Guillemet, C., Delcambre, C., et al., 2015. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. *Lancet Oncol.* 16 (4), 457–464.
  57. Demetri, G.D., von Mehren, M., Jones, R.L., Hensley, M.L., Schuetze, S.M., Staddon, A., et al., 2016. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J. Clin. Oncol.* 34 (8), 786–793.
  58. Schoffski, P., Chawla, S., Maki, R.G., Italiano, A., Gelderblom, H., Choy, E., et al., 2016. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet* 387 (April (10028)), 1629–1637.
  59. Hensley, M.L., Patel, S.R., von Mehren, M., Ganjoo, K., Jones, R.L., Staddon, A., et al., 2017. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: subgroup analysis of a phase 3, randomized clinical trial. *Gynecol. Oncol.* 146 (3), 531–537.
  60. Anderson, S., Aghajanian, C., 2005. Temozolomide in uterine leiomyosarcomas. *Gynecol. Oncol.* 98 (1), 99–103.
  61. Roberts ME, Aynardi JT, Chu CS. *Gynecol Oncol.* Uterine leiomyosarcoma: A review of the literature and update on management options. 2018 Dec;151(3):562-572.