Chapter 3

TREATMENT WITH CELL CYCLE INHIBITORS IN HORMONE POSITIVE METASTATIC BREAST CANCER

Selçuk ŞEBER[1]

The cell cycle is a carefully controlled process in human body and is essential for maintenance and renewal of damaged tissues for functioning organs. However in cancer cells, control of cell cycle is impaired or lost resulting in uncontrolled cell proliferation and avoidance of cell death. Development of agents with the ability of interfering with cell cycle progression in malignant cells is the subject of active investigations. Recent trials in breast cancer patients have shown that cell cycle regulator agents such as selective cyclin dependent kinase (CDK 4/6) inhibitors have important therapeutic effects in metastatic hormone receptor positive breast cancer patients. In this chapter, mechanism of cell cycle regulators , current and potential utilization of CDK 4/6 inhibitors in the management of breast cancer are reviewed.

INTRODUCTION

Breast cancer can be subdivided to different groups by means of expression of hormone receptors,human epidermal growth factor receptor 2 (HER2) overexpression and expression of Ki67 protein. Each of these subgroups carry different prognostic features and therapies and outcomes vary according to the this classification.

Although survival and response rates have greatly improved with the progress made in the field of systemic therapies, recurrence in early stage disease and progression in metastatic cancer remain significant challenges. Standard therapy at advanced stage hormone positive (HR) HER2 negative breast cancer includes anti hormonal agents and chemotherapeutic drugs. The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are the latest agents added to our armamentarium against hormone receptor positive breast cancer. Currently three CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib are in clinical use.

[1] Dr. Öğr. Görev., Namık Kemal Üniversitesi Tıbbi Onkoloji Bilim Dalı, esseber@nku.edu.tr

CONCLUSION

Hormone receptor positive breast cancer represents the largest subgroup of breast cancer spectrum. Although anti hormonal treatment has been largely successful in the metastatic setting development of resistant disease is a rule and drugs which can prolong survival of the HR positive advanced stage breast cancer patients are needed. CDK 4/6 inhibitor therapy by interfering with cell cycle progression has lead to marked prolongation of disease control in this setting and became the new standard of treatment. Understanding resistance mechanisms, identification of sensitive subgroups and discovery of novel agents which an enhance the effectivity of cycle inhibitors other than anti hormonal agents will further strengthen the role of CDK 4/6 inhibitors in the field of cancer treatment.

REFERENCES

1. Abraham J & ark. (2018). Use of cyclin-dependent kinase (CDK) 4/6 inhibitors for hormone receptor-positive, human epidermal growth factor receptor 2-negative, metastatic breast cancer: a roundtable discussion by The Breast Cancer Therapy Expert Group (BCTEG). Breast Cancer Res Treat. 171(1):11-20. doi: 10.1007/s10549-018-4783-1
2. Bardia A, Hurvitz S.(2018). Targeted Therapy for Premenopausal Women with HR(+), HER2(-) Advanced Breast Cancer: Focus on Special Considerations and Latest Advances. Clin Cancer Res. 24(21).5206-18. doi: 10.1158/1078-0432.CCR-18-0162.
3. Barnum KJ, O'Connell MJ. (2014). Cell cycle regulation by checkpoints. Methods Mol Biol. 1170.29-40.
4. Basudan A & ark. (2018). Frequent ESR1 and CDK Pathway Copy-Number Alterations in Metastatic Breast Cancer. Mol Cancer Res. doi: 10.1158/1541-7786.
5. Bower JJ & ark. (2017). Patterns of cell cycle checkpoint deregulation associated with intrinsic molecular subtypes of human breast cancer cells. NPJ Breast Cancer. 3.9.
6. Chappell JC & ark. (2018). Abemaciclib inhibits renal tubular secretion without changing glomerular filtration rate. Clin Pharmacol Ther. doi: 10.1002/cpt.1296.
7. Choo JR, Lee SC.(2018). CDK4-6 inhibitors in breast cancer: current status and future development. Expert Opin Drug Metab Toxicol. 14(11).1123-38. doi: 10.1080/17425255.2018.1541347.
8. Guarducci C & ark. (2017). Mechanisms of Resistance to CDK4/6 Inhibitors in Breast Cancer and Potential Biomarkers of Response. Breast Care (Basel). 12(5).304-08. doi: 10.1159/000484167.
9. Gul A & ark.(2018). A combination of the PI3K pathway inhibitor plus cell cycle pathway inhibitor to combat endocrine resistance in hormone receptor-positive breast cancer: a genomic algorithm-based treatment approach. Am J Cancer Res.8(12).2359-76.
10. Kwapisz D.(2017). Cyclin-dependent kinase 4/6 inhibitors in breast cancer: palbociclib, ribociclib, and abemaciclib. Breast Cancer Res Treat. 166(1):41-54. doi: 10.1007/s10549-017-4385-3.
11. Labib K, De Piccoli G. (2011). Surviving chromosome replication: the many roles of the S-phase checkpoint pathway. Philos Trans R Soc Lond B Biol Sci. 366(1584).3554-61.

12. Loibl S & ark. (2017). Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. Oncologist.22(9):1028-38. doi: 10.1634/theoncologist.2017-0072.
13. Palumbo A, Lau G, Saraceni M.(2018). Abemaciclib: The Newest CDK4/6 Inhibitor for the Treatment of Breast Cancer. Ann Pharmacother. 1060028018795146. doi: 10.1177/1060028018795146.
14. Petrelli F & ark.(2019). Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials. Breast Cancer Res Treat.doi: 10.1007/s10549-019-05133-y.
15. Petrossian K & ark. (2018). ERα-mediated cell cycle progression is an important requisite for CDK4/6 inhibitor response in HR+ breast cancer. Oncotarget. 9(45).27736-51.
16. Rossi L & ark. (2017).Managing advanced HR-positive, HER2-negative breast cancer with CDK4/6 inhibitors in post-menopausal patients: is there a best sequence? Ther Adv Med Oncol.10:1758835918815591. doi: 10.1177/1758835918815591.
17. Shah AN, Cristofanilli M.(2017). The Growing Role of CDK4/6 Inhibitors in Treating Hormone Receptor-Positive Advanced Breast Cancer. Curr Treat Options Oncol. 18(1). doi: 10.1007/s11864-017-0443-7.
18. Shaltiel IA & ark. (2015).The same, only different - DNA damage checkpoints and their reversal throughout the cell cycle. J Cell Sci. 128(4).607-20.
19. Sonke GS & ark.(2017). Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 167(3).659-69. doi: 10.1007/s10549-017-4523-y.
20. Spring LM & ark.(2017). Clinical Management of Potential Toxicities and Drug Interactions Related to Cyclin-Dependent Kinase 4/6 Inhibitors in Breast Cancer: Practical Considerations and Recommendations. Oncologist. 22(9).1039-48. doi: 10.1634/theoncologist.2017-0142.
21. Taylor-Harding B & ark.(2015). Cyclin E1 and RTK/RAS signaling drive CDK inhibitor resistance via activation of E2F and ETS. Oncotarget. 6(2).696-714.
22. Thill M, Schmidt M.(2018). Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer. Ther Adv Med Oncol. 10.1758835918793326. doi: 10.1177/1758835918793326. eCollection 2018. Review. Erratum in: Ther Adv Med Oncol. 2018 Dec 03;10:1758835918810116.