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Review Article

Can CDK 4/6 inhibitors be used in patients with visceral crises? Deviating from conventional teaching

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ABSTRACT

Visceral crisis is a situation in which the vital organ function is impaired due to infiltration by cancer cells. It Is of particular importance in the subset of HR+/Her2- metastatic breast cancer.. Current guidelines that recommend cytotoxic chemotherapy for visceral crisis are based on historical data that indicate that chemotherapy has higher response rates than endocrine therapy. These trials included patients with advanced breast cancer who were not selected for the hormonal receptor or Her 2 receptor status. In addition, the comparator had a weak endocrine agent. Objective response rates with endocrine therapy in combination with any of the CDK 4/6 inhibitors in patients with measurable disease range from 50-59%. These response rates are higher than the chemotherapy rates found in the historical trials. Moreover, patients with visceral crisis have a compromised performance status and impaired organ functions. Therefore, it is unlikely that these patients would tolerate complete doses of the most active chemotherapeutic agents, including anthracycline and taxane. The retrospective analysis of the real-world data base clearly demonstrates that the combination of endocrine agents with a CDK 4/6 inhibitor is superior to chemotherapy with improvement in overall survival. In conclusion, it is time to redefine the guidelines and consider endocrine therapy with a CDK 4/6 combination as the preferred option in the initial management of the visceral crisis.

Keywords: Visceral crisis, Breast cancer, CDK 4/6 inhibitors

DEFINITION OF VISCERAL CRISIS

Cancer endangers life by interfering with the normal functioning of vital organs. The visceral crisis is simply defined as severe dysfunction of vital organs such as liver, lung, brain, or bone marrow due to infiltration by cancer cells. The visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapid efficacious therapy, particularly since another treatment option at progression will probably not be possible.[1]

The ABC5 consensus describes a visceral crisis of the liver and lungs as follows: A visceral crisis of the liver exists when bilirubin levels increase very rapidly (>1.5 times the upper limit of normal) without the presence of Gilbert syndrome or a biliary tract obstruction. A visceral crisis of the lungs can be assumed when dyspnea at rest increases more rapidly and cannot be relieved by pleural drainage.[1] Cytopenia as a result of bone marrow infiltration and leptomeningeal metastases is also regarded as a visceral crisis. This critical condition occurs in approximately 10–15% of patients with advanced breast cancer who receive first-line systemic therapy.[2]

Although visceral crisis can occur with any cancer, it is more pertinent in the subgroup of hormone receptor-positive and HER 2-negative (HR+/HER2–) advanced breast cancer. The

presence of a visceral crisis in this particular subset helps us make a significant therapeutic decision, whether it's chemotherapy or endocrine therapy.[1]

CURRENT GUIDELINES AND THE BASIS OF RECOMMENDATIONS ON THE MANAGEMENT OF VISCERAL CRISIS

The current guidelines recommend cytotoxic chemotherapy rather than endocrine therapy for the treatment of visceral crisis. This is based on the idea that chemotherapy has better and quicker responses than endocrine therapy. There are no randomized trials dedicated to the subset of HR+/HER2− advanced breast cancer patients that report differences in response rates between chemotherapy and endocrine therapy.[3] Randomized trials and meta-analyses that reported better response rates to chemotherapy versus endocrine therapy included patients with advanced breast cancer who were not selected for hormonal receptor status.[3] For example, a randomized trial among postmenopausal women with advanced breast cancer, 75% of whom had an unknown hormone receptor status, reported an overall response rate of 22% with tamoxifen versus 45% with AC chemotherapy. However, the overall survival (OS) was identical in both arms.[4] A meta-analysis reported better response rates to chemotherapy versus endocrine therapy, but the two largest trials in the meta-analysis showed trends in opposite directions, and a test for heterogeneity was significant, thus questioning this observation. Six of the seven trials reported increased toxicity with chemotherapy.[5] In the ECOG 1193 trial, over 700 advanced breast cancer patients unselected for hormone receptor status were randomized to three arms: Doxorubicin plus paclitaxel, doxorubicin, or paclitaxel. The study reported response rates of 47%, 36%, and 34%, respectively.[6]

RATIONALE FOR USING CDK 4/6 INHIBITORS IN VISCERAL CRISIS – DO WE HAVE THE EVIDENCE?

Objective response rates with endocrine therapy in combination with any of the CDK 4/6 inhibitors in patients with measurable disease range from 50% to 59%. These response rates are higher than the chemotherapy rates found in the historical trials. Moreover, the early separation of PFS curves in these trials suggests rapid responses.[7,8]

All breast cancer clinical trials have excluded visceral crisis from the study population. There are just a couple of retrospective studies and case reports on the management of the visceral crisis.

The first one was in the pre-CDK 4/6 era. This retrospective study included 35 HR+/HER2− advanced breast cancer patients with the visceral crisis. They were pre-treated with two lines of endocrine therapy. Postmenopausal women constituted 80% of the population. About 88% of patients had an ECOG performance status 2. Only two-thirds of patients could undergo cytotoxic chemotherapy. Most of them received just 1 cycle of chemotherapy. The mean time between visceral crisis and death was 4.7 weeks. It concluded that chemotherapy had no significant impact on patient outcomes.[2]

Another retrospective study of HR+/HER2− metastatic breast cancer patients in visceral crisis reported that chemotherapy confers no survival advantage when compared to supportive care (5.8 weeks vs. 6.2 weeks, $P = 0.23$).[2]

The best evidence for the management of visceral crisis comes from a retrospective analysis of a real-world database. The goal of this study was to look at the efficacy of CDK 4/6 inhibitors among HR+/HER2− metastatic breast cancer patients who present with the visceral crisis at diagnosis. This included a total of 336 patients in visceral crisis 0.61 (18%) received CDK4/6 inhibitor therapy as first-line therapy. Propensity score matching was performed on all comparisons of survival. Median OS among patients who did and did not receive CDK 4/6i was 11 months and 6 months, respectively ($P = 0.01$). Two-year OS was 26.1% for patients who received CDK 4/6i and 8.1% for those who received chemotherapy. The use of CDK4/6i in the presence of visceral crisis at diagnosis was associated with a 5-month improvement in OS compared to chemotherapy.[9]

VISCERAL CRISIS WITH HEPATIC DYSFUNCTION – A UNIQUE CHALLENGE

Patients with the visceral crisis with hepatic dysfunction, in particular, pose a unique challenge in the management. This is because the most active chemotherapeutic agents, namely, anthracyclines and taxanes are extensively metabolized in the liver. Consequently, the use of these agents at adequate doses would not be feasible. Endocrine therapy in combination with a CDK 4/6i can be safely administered in this situation. For example, for abemaciclib, no dosage adjustments are necessary for patients with mild or moderate hepatic impairment (Child-Pugh A or B). We need to reduce the dosing frequency in patients with severe hepatic impairment (Child-Pugh C). For ribocilcib, no dose adjustment is necessary for mild hepatic impairment (Child-Pugh Class A). The recommended starting dose is 400 mg once daily for patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C). In the case of a heavily pre-treated endocrine-resistant disease and if the patient qualifies for chemotherapy, the combination of platinum and fluoropyrimidine is reasonably safe in these circumstances.

SUMMARY AND CONCLUSION

The treatment of visceral crisis is best described as a last-ditch effort to salvage the endangered vital organ. An extremely wise and judicious choice of the systemic therapeutic agent which is most effective and least toxic must be made. This is because if the disease progresses or if the patient develops toxicity, it is unlikely the patient remains eligible for further anticancer therapy.

The current guidelines that recommend cytotoxic chemotherapy for the visceral crisis are based on historical data that indicates that chemotherapy has higher response rates than endocrine therapy. These trials included patients with advanced breast cancer who were not selected for the hormonal receptor or HER-2 receptor status. In addition, the comparator had a weak endocrine agent. Moreover, patients with the visceral crisis have a compromised performance status and impaired organ functions. Therefore, it is unlikely that these patients would tolerate complete doses of the most active chemotherapeutic agents, including anthracycline and taxane. The retrospective analysis of the real-world database demonstrates that the combination of endocrine agents with a CDK 4/6 inhibitor is superior to chemotherapy with an improvement in OS. In conclusion, it is time to redefine the guidelines and consider endocrine therapy with a CDK 4/6 combination as the preferred option in the initial management of the visceral crisis.

Declaration of patient consent

Patient consent is not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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