Triple therapy for metastatic castration sensitive prostate cancer: PEACE-1 trial

Kirti Singh*
Department of Urology, AIIMS, Bhubaneswar, Odisha, India
*E-mail: kirtisingh2604@gmail.com

SUMMARY

PEACE-1\(^1\) was a multicenter, open-label, phase-3 randomized controlled trial (RCT) undertaken by the PEACE European consortium. It enrolled 1173 men from seven countries with synchronous (de novo) metastatic hormone sensitive prostate cancer (mCSPC), who were randomly assigned in a 1:1:1:1 ratio to receive SOC (standard of care, i.e., ADT with docetaxel), SOC + RT, SOC + abiraterone (AP), or SOC + RT + AP (i.e., abiraterone + prednisolone). A randomized 2 × 2 factorial design was used to compare radiotherapy (RT) to primary tumor against AP + RT. The co-primary endpoints were overall survival (OS) and radiographic progression-free survival (RPFS). Adjusted cox regression modeling revealed no interaction between AP and RT; this allowed the pooled analysis of AP efficacy. Notable findings of PEACE-1 include the following - Trial showed an advantage of two and half years (2 years with SOC vs. 4.5 years with the addition of AP) for RPFS. OS was improved with a 25% reduction in risk of death, even when 84% of mCSPC men in the control group receive at least one life-prolonging treatment. The incidence of grade 3–5 neutropenia and febrile neutropenia was comparable between the two groups, at 10% versus 9% and 5% versus 5%, respectively, but the rates of hypertension and transaminase elevations were higher, at 22% versus 13% and 6% versus 1%, respectively.

This RCT concluded that combining SOC with AP improved both co-primary endpoints of OS (hazard ratio [HR] = 0.82) only in high-volume disease and RPFS (HR = 0.54).

COMMENTS

The focus of recent advances in carcinoma prostate has now shifted from the management of castrate resistant to castrate-sensitive patients. The ideal combination of various agents in setting of mCSPC has still not been assessed. for high-volume mCSPC, the addition of AP (+prednisolone) to SOC makes sense. Till date, PEACE-1 is the only phase 3 trial to show that a triple systemic therapy, combining ADT, docetaxel, and AP improves both OS and RPFS in patients with de novo mCSPC without significantly increasing toxicity.

The current SOC is ADT + Docetaxel.\(^2\) It is based on the results of a systematic review and meta-analysis by Sathianathen et al., in 2018\(^3\) which included STAMPEDE, GETUG, and CHAARTED trials. STOPCAP systemic review and meta-analysis\(^4\) showed that AP has the highest probability of success. Based on the above two meta-analyses, the addition of AP to ADT + Doctaxel is a good proposition as done in PEACE-1.

PEACE-1 trial showed survival advantage as AP improves OS, while docetaxel (D) retains some efficacy even after AP failure also concomitant administration (AP + D) did not lead to an increase in side effects or hematological toxicity.

A similar ongoing phase 3 trial ARASENS\(^5\) is assessing efficacy of darolutamide with ADT and docetaxel.

PEACE-1 had a complicated design that was made even more complicated by its modifications. The trial is still ongoing and the results of secondary endpoints are not reported yet, and the efficacy of RT remains unanalyzed. Formal analysis of quality of life data is still pending which will tell the impact of toxicity on participants and we eagerly wait for the final results of this trial as it will be helpful to obtain a piece of concrete evidence for hormonal therapy in mCSPC and further enhance the level of evidence what is present.

The crucial questions that remained to be answered are - If there is a subset of individuals who do not require such an aggressive treatment regimen and if de-escalation after a good response with the prescribed treatment regimen could have any bearing on the survival outcomes. These will necessitate well-designed clinical trials in future.

This trial points toward the need to escalate treatment in patients with high-volume mCSPC. AP is available commonly even in developing countries. The addition of...
AP to SOC can be vastly beneficial, especially in developing countries like ours where the majority of the patients present with high-volume disease. However, the application of this regimen in various subsets such as metachronous metastasis or long-term benefit in high- versus low-volume disease still remains to be seen. Furthermore, many a times, SOC to start with is ADT + AP. Hence, based on the study design, this trial would not be able to answer the triplet therapy by adding docetaxel to ADT + AP. Biomarkers which can identify patients at the highest risk of disease progression to mCRPC may further help in recommending triplet therapy in mCSPC patients.

Future superiority trials may add evidence regarding the true value of triplet therapy. With longer follow-up data, triplet therapy may soon become the treatment of choice for mCSPC.

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