Docetaxel and Estramustine Chemotherapy plus Androgen-Deprivation Therapy Improves Relapse-Free Survival in Patients with High-Risk Localized Prostate Cancer

BACKGROUND: The current treatment landscape for patients with high-risk localized prostate cancer is predominantly confined to a combination of androgen-deprivation therapy (ADT) plus radiotherapy, which has been shown to improve survival over radiotherapy alone. Although risk-based chemotherapy is a standard approach to treatment in breast, colon, and lung cancers, few trials have assessed the use of chemotherapy for patients with high-risk localized prostate cancer. Now a new study evaluated the addition of docetaxel-based chemotherapy to ADT for patients with high-risk localized prostate cancer.

Previous studies have demonstrated that docetaxel, with or without estramustine, results in improved outcomes, including survival, in patients with metastatic castration-resistant prostate cancer. These findings have led Fizazi and colleagues to conduct the phase 3, randomized, controlled clinical trial known as GETUG 12, which evaluated the efficacy of docetaxel plus estramustine and ADT versus ADT alone in patients with high-risk localized prostate cancer. The preliminary results showed improved prostate-specific antigen (PSA) response and no negative effect on the patient’s quality of life with the combination therapy compared with ADT alone.

METHODS: This latest report from GETUG 12 was focused on relapse-free survival—which is defined as biochemical failure, onset of metastases, proven local relapse, use of salvage treatment, and death—in patients with high-risk localized prostate cancer. The trial was conducted at 26 hospitals in France, and enrolled patients with treatment-naive prostate cancer and ≥1 risk factors, including T3 to T4 disease, a Gleason score of ≥8, PSA >20 ng/mL, or pathologic node-positive disease. Overall, 207 patients received the docetaxel plus estramustine and ADT combination and 206 patients received ADT alone, with a median follow-up of 8.8 years.

RESULTS: Overall, the rate of disease relapse or death was 43% among patients receiving the chemotherapy-based combination therapy compared with 54% among patients who received ADT alone. In addition, the 8-year relapse-free survival was 62% in the chemotherapy group versus 50% in the ADT-alone group, and biochemical failure was the most common relapse event.

The chemotherapy was well-tolerated, and grade ≥2 adverse events were comparable between the 2 groups. Furthermore, there was no excess of secondary cancers, and no leukemia was reported in the chemotherapy group. According to Fizazi and colleagues, testosterone recovery after stopping ADT is not likely to be the reason for the benefits of chemotherapy on relapse-free survival, because analysis of serum testosterone showed no difference between the 2 groups; further analysis will help to elucidate the patterns of relapse.

The use of docetaxel-based chemotherapy with ADT is a viable treatment option for patients without castration-resistant disease; however, additional studies and longer follow-up are needed to confirm that relapse-free survival results in improved metastasis-free survival and overall survival in patients with high-risk localized prostate cancer.


COMMENTARY BY ROBERT J. IGNOFFO

This study had a long follow-up period and is the first large, randomized study demonstrating the benefit of adding combination chemotherapy to ADT in patients with high-risk prostate cancer. The greatest benefit was observed in patients with elevated PSA, positive lymph nodes, and T3 to T4 disease, but not in patients with PSAs >8. Although not statistically significant, there were fewer deaths caused by prostate cancer progression in the combination group than in the ADT-only group. Furthermore, the combination resulted in no treatment-related deaths or second malignancies. In addition, grade 2 or higher toxicities were similar to the ADT-only group in
Hepatocellular Carcinoma After First-Line Sorafenib for Advanced Tumor Progression

The 87% of patients who received radiotherapy. However, this study did not evaluate long-term cardiovascular events. Acute adverse effects were reported in a companion study and included febrile neutropenia (2%) in the chemotherapy combination. Moderate-to-severe hot flashes occurred less often in the combination group (2% vs 22%; P <.001). There was a negative impact on quality of life at 3 months into chemotherapy, but this effect disappeared at 1 year.

Although this study validates the role of chemotherapy in patients with high-risk prostate cancer and may be considered as another therapeutic option, patients and caregivers may need to decide whether this combination will offer a clinically significant benefit.


Second-Line Treatment with Ramucirumab After First-Line Sorafenib for Advanced Hepatocellular Carcinoma

BACKGROUND: Hepatocellular carcinoma is the second most common cause of cancer-related death and occurs most often in patients with cirrhosis. Vascular endothelial growth factor (VEGF) plays an important role in tumor growth and angiogenesis, and is overexpressed in patients with hepatocellular carcinoma. The treatment options for this patient population are limited; sorafenib is the only drug that has shown improved median overall survival (OS). However, sorafenib is associated with significant toxicities. Previous studies with ramucirumab, a VEGF inhibitor, demonstrated antitumor activity in patients with hepatocellular carcinoma and in those with renal-cell carcinoma after sorafenib therapy. A REACH study assessed the safety and efficacy of ramucirumab in patients with advanced hepatocellular carcinoma after first-line therapy with sorafenib.

METHODS: REACH was a randomized, double-blind, multicenter, phase 3 clinical trial of 565 patients with hepatocellular carcinoma who had received sorafenib and were randomized in a 1:1 ratio to receive ramucirumab 8 mg/kg or placebo every 2 weeks. The primary end point was OS; the secondary end points included the median progression-free survival (PFS), time to tumor progression, and objective response.

RESULTS: Treatment with ramucirumab did not significantly improve OS compared with placebo; the median OS was 9.2 months with ramucirumab versus 7.6 months with placebo. Nevertheless, Zhu and colleagues reported improvements in the secondary end points. The median PFS was 2.8 months with ramucirumab compared with 2.1 months with placebo; the median time to tumor progression was 3.5 months with ramucirumab versus 2.6 months with placebo, and an objective response was reported in 7% of patients receiving ramucirumab compared with <1% of patients receiving placebo. The safety profile of ramucirumab was consistent with previous studies.

Although REACH did not meet its primary end point of OS, the study yielded a particularly noteworthy finding. A subgroup analysis showed that ramucirumab was especially effective at improving OS in patients with a baseline α-fetoprotein concentration of ≥400 ng/mL, where the median OS was 7.8 months with ramucirumab versus 4.2 months in the placebo group. Elevated α-fetoprotein concentration is associated with poor prognosis in hepatocellular carcinoma, and the conferred benefit with ramucirumab in patients with an elevated α-fetoprotein concentration bolsters support for targeting angiogenesis in advanced hepatocellular cancer.

In addition, Zhu and colleagues postulated that elevated α-fetoprotein concentrations may help to identify patients who would benefit most from ramucirumab therapy; further studies are needed to confirm this hypothesis.


COMMENTARY BY ROBERT J. IGNOFFO

Unfortunately, this study by Zhu and colleagues did not show significantly improved OS. The authors looked for differences in secondary end points and found that PFS was significantly prolonged but only by approximately 1 month. They also performed a Forrest plot of secondary end points and found that high levels of the surrogate marker, α-fetoprotein, were associated with significant improvement in OS with a hazard ratio of 0.67. However, until these results are further substantiated in other studies, the use of ramucirumab as second-line therapy for patients with hepatocellular carcinoma is not recommended.
Everolimus Improves Outcomes When Added to Trastuzumab and Paclitaxel as First-Line Therapy in HR-Negative, HER2-Positive Advanced Breast Cancer

BACKGROUND: Resistance to trastuzumab is a common problem for patients with HER2-positive breast cancer. Previous studies have shown that adding mTOR inhibition with everolimus to trastuzumab-based therapy provided clinical benefits in heavily pretreated patients with HER2-positive advanced breast cancer who had disease progression. This led to the launch of 2 phase 3 clinical trials, BOLERO-1 and BOLERO-3. BOLERO-3 showed a significant improvement in progression-free survival (PFS) with the addition of everolimus in patients whose disease had progressed with trastuzumab-based therapy. The benefits of everolimus were especially pronounced in patients with hormone receptor (HR)-negative tumors. BOLERO-1 compared the use of everolimus as first-line treatment in the full patient population and in the HR-negative subpopulation.

METHODS: In the BOLERO-1 phase 3, randomized, double-blind, multicenter clinical trial, 719 patients with HER2-positive advanced breast cancer who had not received therapy with trastuzumab or chemotherapy for advanced breast cancer were randomized in a 2:1 ratio to receive everolimus 10 mg or placebo once daily plus trastuzumab and paclitaxel, with a median follow-up of 41.3 months.

RESULTS: PFS in the full patient population was 14.95 months with everolimus versus 14.49 months with placebo, indicating no significant differences between the 2 groups. However, the difference in PFS, although also not significant, was markedly evident in the HR-negative subpopulation at 20.27 months with everolimus versus 13.08 months with placebo. Hurvitz and colleagues noted that the threshold for statistical significance in the HR-negative subpopulation was stringent. The toxicity profile of everolimus-based therapy was consistent with that of previous studies. Because the 3-drug combination is associated with a high incidence of adverse events, monitoring and managing these events is essential.

The findings from BOLERO-1 support the data from BOLERO-3, suggesting that adding everolimus to trastuzumab and paclitaxel may be a first-line therapy option for patients with HR-negative, HER2-positive advanced breast cancer. Ongoing studies are evaluating the benefits of adding PI3K/mTOR inhibitors to endocrine therapy and HER2-targeted therapy for patients with HR-positive, HER2-positive advanced breast cancer.

Daratumumab Monotherapy Effective in Patients with Relapsed Myeloma

BACKGROUND: Proteasome inhibitors and immunomodulatory agents can improve the outcomes of patients with multiple myeloma, but the majority of these patients experience relapse and consequently have limited treatment options. However, myeloma cells highly and uniformly overexpress CD38. Daratumumab is a CD38-targeting, human IgG1 monoclonal antibody. In a 2-part, phase 1/2, open-label, multicenter trial, researchers studied the efficacy of daratumumab monotherapy in patients with relapsed myeloma or relapsed myeloma that was refractory to 2 or more previous lines of therapy.

METHODS: Part 1 of the trial was a dose-escalation study and part 2 was a dose-expansion study. In part 1, patients in 10 cohorts received doses of 0.005 mg to 24 mg of daratumumab per kilogram of body weight. Pre-dosing on the day before the first 2 full infusions was intended to minimize the risk of infusion-related reactions. In part 2, 8-mg/kg and 16-mg/kg doses of daratumumab were administered with different schedules that were labeled A, B, C, D, or E. Patients received the therapy until disease progression or until toxic events became unmanageable. The primary end point was safety, which was determined by the frequency and severity of adverse events.

COMMENTARY BY ROBERT J. IGNOFFO

As indicated in the current National Comprehensive Cancer Network Guidelines, first-line therapy options for HR-negative, HER2-positive advanced breast cancer include (1) pertuzumab plus trastuzumab plus docetaxel (Category 1A) or (2) pertuzumab plus trastuzumab plus paclitaxel (Category 2A). Both PFS and overall survival (OS) were significantly improved in phase 3 trials. While the authors of BOLERO-1 demonstrate significant improvement in PFS, they do not report OS despite its inclusion as a secondary end point (probably because not enough events occurred for an interim analysis). Before the regimen of everolimus plus trastuzumab plus docetaxel can be put forth as first-line therapy, results concerning OS should be reported and should demonstrate significant benefit.
RESULTS: A total of 32 patients were enrolled in part 1 of the trial and had a median of 4 previous treatments. No maximum tolerated dose was found, and dose-limiting toxic events were observed at doses of 0.1 mg/kg and 1 mg/kg. After treating 3 additional patients at these dose levels with no further dose-limiting toxic events, the dose level was escalated to 24 mg/kg. A total of 33% of patients had a partial response when they received doses of 4 mg/kg to 24 mg/kg in this part of the trial.

In part 2, 72 patients were enrolled. Infusion-related reactions occurred in 71% of patients and were grade 1 or 2, except in 1 patient receiving the schedule E regimen who had grade 3 reactions. No patient discontinued treatment because of an infusion-related reaction. The frequency of infusion-related reactions was lower in the cohort that followed the schedule C first-infusion regimen (8 mg/kg in 1000 mL for 6 hours) than in the other cohorts, suggesting that the infusion rate may be significant in managing infusion-related reactions. The most common adverse events observed were fatigue, allergic rhinitis, and pyrexia. The overall response rate was 36% in patients who received 16 mg/kg, with 2 patients having a complete response, 2 having a very good partial response, and 11 having a partial response. The overall response rate was higher in patients who had received 2 or 3 prior lines of therapy (56%) than in more heavily pretreated patients (23%). The estimated median progression-free survival was 2.4 months (95% confidence interval [CI], 1.4-3.5) in the cohort that received 8 mg/kg and 5.6 months (95% CI, 4.2-8.1) in the cohort that received 16 mg/kg. The overall survival rate at 12 months was 77% (95% CI, 52-90) in the cohort that received 8 mg/kg and 77% (95% CI, 58-88) in the cohort that received 16 mg/kg.

Overall, daratumumab had an acceptable safety profile and showed encouraging efficacy in patients with myeloma who had previously received 4 lines of therapy. Daratumumab may be an effective single-agent therapy for patients with relapsed or relapsed and refractory myeloma, especially for patients who were resistant to or experienced unmanageable side effects with previous treatments.


COMMENTARY BY ROBERT J. IGNOFFO

Multiple myeloma is an indolent disease that continues to respond to multiple combination therapies, even in patients who have become refractory to several first-line therapies, including stem-cell transplant. Other first-line therapies include bortezomib-, lenalidomide-, or dexamethasone-based therapy. Daratumumab offers a different mechanism of action and appears to be effective and relatively safe. This phase 1/2 study only presented data on 42 patients. Of note is the high incidence of infusion-related events (71%) and the duration of administration (6.5-8 hours for the first infusion); these will greatly impact outpatient nursing administration and toxicity management. Until a more extensive phase 2 or phase 3 study is performed, daratumumab is relegated to a lower line of therapy.
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