Unexpectedly good results, and no chemotherapy required

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Cabozantinib in metastatic prostate cancer[1,2]

Researchers tested cabozantinib, a tyrosine-kinase inhibitor (TKI) against MET and vascular endothelial growth factor receptor 2 (VEGF), in a large phase 2 randomized discontinuation trial in 9 tumor types. A subset of 171 patients with castrate-resistant prostate cancer (CRPC) was reported in this study. Patients were treated on open label for 12 weeks, and then if stable, were randomized to receive the active drug or placebo.

The trial was suspended early by the study oversight committee because:

a) Cabozantinib was too toxic for the study to continue.
b) The prostate-specific antigen (PSA) level fell in most of the treated patients.
c) In the initial 121 patients, there was an unexpected improvement in bone scans and decrease in pain in the lead-in stage of the study.
d) Unexpected rapid soft tissue progression.

Bone scans improved in 78% of patients, and in 12% there was complete remission. After further analysis, the following were true except for:

a) Cabozantinib interfered with technetium-99, and thus, the responses were not real, but rather an artifact.
b) The PSA did not correlate with improvement in bone pain.
c) Markers of bone formation and resorption showed improvement, and there was no correlation with prior bisphosphonate therapy.
d) Bone scan improvement correlated with improvement in soft tissue disease.

Key points

The results in patients with prostate cancer were so striking – 72% of patients had regression in soft tissue lesions, and 68% of evaluable patients had improvement on bone scan, including complete resolution in 12% – that the subset analysis was published as a rapid communication.[1,2] Because of very high response rates (5% at 12 weeks) and symptomatic improvement in the initial 122 patients who were enrolled, random assignment was discontinued. Bone markers improved in concert with the radiologic and clinical improvement.

Answers c, a

The CYTO-PV study[3,4]

Current guidelines for the treatment of polycythemia vera suggest a target hemoglobin of 45%, although until 2013 there was no level 1 evidence for this practice. In the CYTO-PV study, 365 adults with polycythemia vera were randomized to receive more intensive cytoreductive therapy to achieve a target hematocrit of less than 45% or to receive less intensive therapy to achieve a target hematocrit of 45%-50%. It is difficult to believe that after all these years the simple non-pharmacologic therapeutic intervention of phlebotomy has finally been shown to have a statistically significant effect on an important clinical endpoint in this large, multicenter, prospective, randomized clinical trial of patients with polycythemia vera.

The primary result of this study in terms of the clinical endpoint included all of the following, except:

a) In patients maintaining the target hematocrit of 45%-50%, there was a 4-fold increase in death from cardiovascular causes and major thrombosis compared with patients maintaining the target hematocrit of less than 45%.
b) Women who achieved a target hematocrit of < 42% had a benefit similar to that of men who achieved a target hematocrit of < 45%.
c) Progression to myelofibrosis, myelodysplasia, or leukemic transformation, and the development of solid tumors was nonsignificantly increased in the low hematocrit group.

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d) The specific type of cytoreductive therapy was not a significant factor in terms of the endpoints.

Clinical and laboratory parameters of interest in the study results included:
a) Almost all of the patients were JAK1 positive.
b) All of the patients were red-blooded Americans.
c) 50% of the patients were men.
d) The risk of primary endpoint was higher for patients with a white blood cell count of > 8,600 cells/μL.

Key points

Polycythemia vera is a myeloproliferative disease characterized by panmyelosis, an increase in red cell mass, and a consequent high risk of thrombosis. Management recommendations have included lowering the hematocrit to decrease thromboembolic and cardiovascular events. The current study was a prospective, randomized, multicenter trial conducted in Italian medical centers. The primary endpoint of death from cardiovascular causes or major thrombotic events was 4 times more likely in patients in the high hematocrit group (target hematocrit, 45%-50%), compared with the low hematocrit group (target hematocrit, < 45%). The specific regimen (phlebotomy or drug) was not significant, nor was the pretreatment white blood cell count or platelet count. In all, 62% of the patients were men, and there was no lower target hematocrit for the women entered on this trial (even though some guidelines recommend a target hematocrit of 42% for women). In this study, only 75% of patients received aspirin therapy, but the use of aspirin in this trial was not a significant factor.

Answers b, a

Targeting BTK in CLL and mantle cell lymphoma[5-8]

Two remarkable phase 2 studies of targeted treatment for refractory B-cell disorders were published recently. Bruton's tyrosine kinase (BTK) is an important mediator of B-cell signaling. Ibrutinib is an oral inhibitor of BTK. In both chronic lymphocytic leukemia (CLL) and mantle cell lymphoma, ibrutinib was shown to have significant activity in relapsed and refractory patients. It was recently approved by the Food and Drug Administration for patients with mantle cell lymphoma who have received at least one prior therapy.

In the phase 1b-2 study in refractory CLL, the results included all of the following, except:
a) High overall response rate and high complete response rate.
b) Response was independent of 17P13.1 deletion or unmutated immunoglobulin status.
c) There was no dose-response relationship for ibrutinib.
d) The progression-free survival was 75% and overall survival 83% at 26 months.

In the phase 2 study in mantle cell lymphoma, the results included all of the following, except:
a) The overall survival was 58% at 18 months.
b) Overall response rate of 68% with complete response rate of 21%.
c) A lower response rate was observed in patients who had previous bortezomib or lenalidomide therapy.
d) A substantial increase in mantle cells in the peripheral blood 10 days after treatment.

A comparison for the 2 studies indicated:
a) A late toxicity of agammaglobulinemia, similar to Bruton's x-linked agammaglobulinemia, occurred in CLL and mantle cell lymphoma patients.
b) The complete response rate was higher in the mantle cell study than in the CLL study.
c) Grade 3 or higher hematologic toxicity was prevalent in both diseases.
d) BTK has an oncogenic driver role in both CLL and mantle cell lymphoma.

Key points

Mutations in BTK cause X-linked agammaglobulinemia. BTK is a part of downstream signaling of the B-cell receptor and may be essential for CLL-cell survival. Although spleen tyrosine kinase (SYK) may not play an oncogenic driver role in mantle-cell lymphoma, it is amplified in this disease and BTK is an important component of the pathway downstream of SYK. In the study of ibrutinib in CLL, there was a high overall response rate, but the complete response rate was quite low, whereas among mantle cell patients there was a similar overall response rate but a significant complete response rate. Response rates were not lower in high risk CLL patients with 17p13.1 deletions or unmutated immunoglobulin status, or in mantle cell patients with previous therapy with bortezomib or lenalidomide. Lymphocytosis was observed in the CLL patients, and there was an increase in peripheral blood mantle cells in the mantle cell lymphoma patients. There was no reduction in immunoglobulin levels in either study. Toxicities were primarily nonhematologic.

Answers: a, c, b

Retinoic acid and arsenic for APL[9-11]

All-trans retinoic acid (ATRA) was discovered empirically in the 1980s as a nonchemotherapy treatment for acute promyelocytic leukemia (APL) and is one of the earliest forms of targeted therapy. Targeting the promy-

elocytic leukemia-retinoic acid receptor (PML-RARA), ATRA has been combined with chemotherapy for the first-line therapy of the disease. Arsenic trioxide also targets PML-RARA but it has been traditionally used as salvage therapy for patients failing first-line therapy. ATRA and arsenic were thought to be antagonistic for effects on differentiation of PML cells, but later found to be highly synergistic in leukemia-initiating activity. This new information led to combination therapy using the 2 targeted agents together instead of the standard ATRA plus chemotherapy. The former approach (ATRA-arsenic trioxide) was at least as effective and possibly more effective than ATRA-chemotherapy.

In this phase 3, multicenter, randomized trial, ATRA plus chemotherapy was compared with ATRA plus arsenic trioxide in patients with low-to-intermediate risk APL. The efficacy results included all of the following, except:

a) Two-year event-free survival was better for ATRA-arsenic.
b) Overall survival that was superior for ATRA-arsenic.
c) Complete remission that was superior to ATRA-arsenic.
d) Log reduction in PML-RARA transcripts was the same in both arms of the study.

Which information below was not mentioned in the NEJM paper[9] or supplementary material on the NEJM website:

a) Alopecia occurring in most patients on the ATRA-chemotherapy arm of the study.
b) 63% of the ATRA-arsenic treated patients had grade 3 or 4 hepatic toxicity.
c) Grade 3 or 4 neutropenia lasting more than 15 days was significantly more frequent in the ATRA-chemotherapy arm.
d) QTc prolongation occurred in 16% of the ATRA-arsenic arm, but in no patients treated with ATRA-chemotherapy.
e) In the 1944 movie, *Arsenic and Old Lace*, Cary Grant's homicidal maiden aunts combined arsenic with strychnine rather than ATRA and a pinch of cyanide in a glass elderberry wine. None of the victims had leukemia.

Key points

The combination of ATRA and arsenic had much less hematologic toxicity than ATRA-chemotherapy, but there was significant hepatic toxicity, and some ECG changes. Alopecia was not mentioned in the paper or supplemental material, but presumably there would have been significant alopecia in the patients receiving idarubicin. Although the complete remission rate and reduction in PML-RARA transcripts was not superior in the ATRA and arsenic arm, the 2-year even-free survival and overall survival was superior. Because of this, the authors felt that the nonchemotherapy combination was at least noninferior and possibly superior to ATRA plus chemotherapy. Finally, Cary Grant's crazy aunts did not combine ATRA with arsenic trioxide, but rather elemental arsenic with strychnine, and a pinch of cyanide, and this was absolutely not mentioned in the NEJM paper.

Answers c, a and e

Combination checkpoint blockade in melanoma[12-14]

In 2010, we learned that ipilimumab, which blocks CTLA-4 and potentiates the T-cell antitumor activity, markedly improved overall survival in patients with refractory metastatic melanoma.[12] Two years later, 2 large phase 1 studies showed significant antitumor effects in metastatic melanoma for the antibody blockade of the interaction between the programmed death 1 protein (PD-1) and its ligand (PD-L1) on T-cell inhibition. In the current study, a combination of dual checkpoint blockade was carried out in patients with metastatic melanoma.[13]

Combining the antibodies to provide dual blockade of inhibitory pathways for tumor-specific T-cells resulted in all of the following, except:

a) Overall clinical benefit in patients receiving concurrent therapy was 65%.
b) Overall response rate was 40%.
c) Serious adverse events were rare.
d) Virtually all of the patients suffered adverse events.

2. Which of the following seemed to be a result of combined checkpoint blockade compared with using a single agent:

a) Increase in toxicity compared with single agents of this type.
b) Deeper responses (> 80% reduction of tumor bulk).
c) Concurrent therapy did not seem to produce more striking waterfall and "spider" plots compared with sequential therapy.
d) More patients had to mortgage their houses to pay for the therapy.
e) Infusion-related reactions were more common.

Key points

Combination immune checkpoint blockade that enables tumor-specific T-cells to be activated utilizing a combination of antibodies to both CTLA-4 and PD-1 resulted

in a higher clinical benefit rate than expected in this population of patients with metastatic melanoma. Even though this was a phase 1 trial, the therapeutic effects were striking, with an overall clinical benefit rate of 65% and overall response rate of 40%. Almost all the patients suffered some sort of adverse events, and serious adverse events occurred in 49% of the patients. However, the adverse event experience was similar to previous experience with monotherapy. The deeper response rates and more striking spider and waterfall plots of response were impressive, even in this relatively small study. Infusion reactions were rare. The overall cost of this type of treatment is yet to be determined, but as this was an investigational study, no participant had to put a second mortgage on his or her home.

Answers c, b

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