

The importance of cellular pathways and updates on anti-angiogenic drugs

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Today's morning session started off with a heavy dose of basic science--two important pathways were discussed. One is a key driver of cell growth that originates from growth factor receptors and is transmitted through an enzyme called PI3 kinase. This pivotal enzyme is regulated (or turned off) by another enzyme called PTEN. It turns out that there are mutations in PI3 kinase as well as PTEN that can deregulate this pathway and lead to cell growth and also resistance to growth factor receptor antibody drugs. While we are years away from new therapies in the clinic, there are already PI3 kinase inhibitors in clinical trials.

Another pathway is less understood and leads to a cellular transformation termed epithelial-mesenchymal transition, whereby tumor cells may actually evolve into more difficult to treat cancer stem cells. Stem cells are thought to be responsible for recurrence and drug resistance, but newer drugs that target stem cells are now in clinical trials. Dr. Jenny Chang presented both animal and human clinical trial tissue-based data that preliminary shows effectiveness of these drugs at the cell level. Of course, the final proof of these drugs will be in later trials that will be ongoing over the next few years.

The afternoon session reviewed a follow-up of a trial of Avastin that showed an improvement in progression-free (but not overall) survival when added to the chemotherapy Taxotere for metastatic breast cancer--confirming early results. A newly presented trial, Ribbon II, examined Avastin in patients who had already received chemotherapy for advanced disease (second line) and showed that in this situation, Avastin can also delay progression when added to several types of chemotherapy (taxanes and capecitabine). This might expand the settings in which Avastin can be used, but several audience members questioned whether the lack of a survival benefit should justify the routine use of Avastin.

New anti-angiogenic kinase inhibitors are being tested in addition to chemotherapy and two trials of the drug Nexavar, already approved for kidney cancer, were tested in addition to Xeloda or Taxol in two separate studies, compared to chemotherapy alone. The Taxol study showed a very slight benefit, but the Xeloda study showed a clear improvement in progression-free survival. Both of these were smaller trials and not the type that the FDA would review for approval, but will probably lead to more definitive studies. In both cases, side effects were rather prominent, especially with hand/foot syndrome seen in the Xeloda study--although the presenting investigator, Dr. Jose Baselga, felt that these could be lessened with closer monitoring and more rapid dose adjustments. The general theme of how small of a benefit is worthwhile was again brought up--especially in light of the side effects. The larger trials will have formal quality of life analyses. Another anti-angiogenic kinase inhibitor, sunitinib, also already approved in kidney cancer was compared to Xeloda, both drugs given by

themselves, and somewhat surprisingly, Xeloda was better than sunitinib. So this drug will probably not be further developed for breast cancer, at least not as a single agent.

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