Clin. Invest. (2013) 3(12), 1109–1111

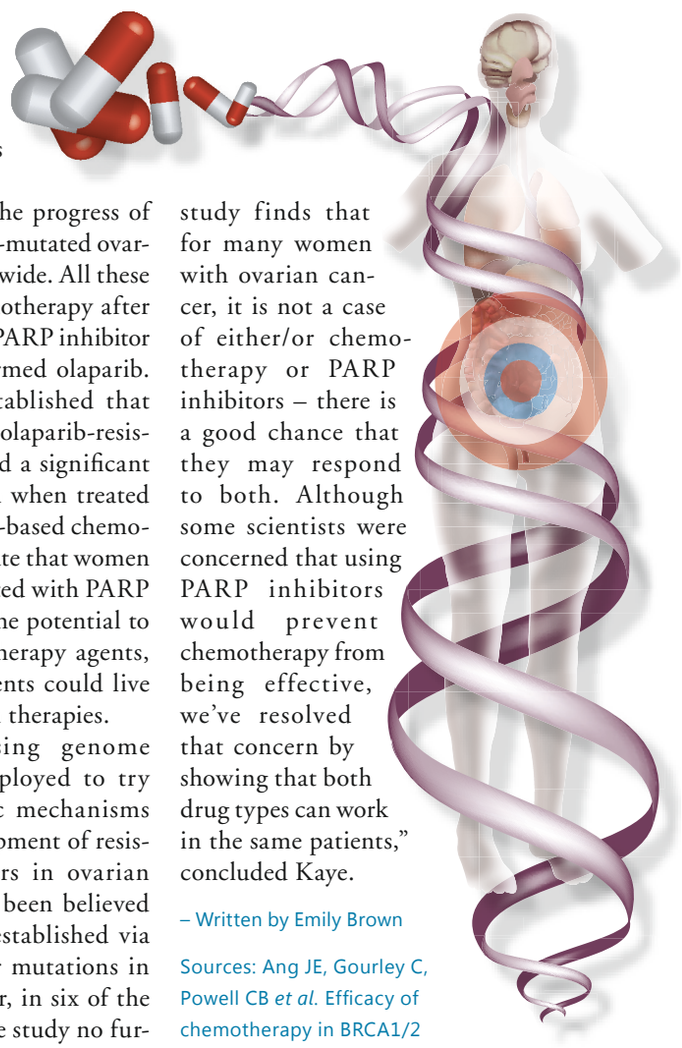
CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

New evidence supports tandem treatment in some ovarian cancers

A total of 89 individuals included in clinical study of PARP inhibitors plus chemotherapy in ovarian cancer



The results of a new study may provide evidence that PARP inhibitors and chemotherapy can be effective in the same patient, further extending the life of some individuals with ovarian cancer when used in tandem. PARP inhibitors are a relatively new targeted therapy being developed in clinical trials worldwide, particularly for use in women with *BRCA* gene mutations, and are particularly favorable as they are associated with less toxic side effects than conventional chemotherapy.

"Ovarian cancer is a difficult disease to treat and our research does underline the complexity of cancer, and the many different routes it can use to become resistant to treatment. But it also presents us with an opportunity, by showing us that two different types of drug treatment given in sequence could potentially extend lives," explained Stan Kaye of the Institute of Cancer Research (London, UK), leader of the study.

Kaye and colleagues investigated follow-up data from previous clinical trials in order to ascertain the efficacy of conventional chemotherapy regimens in ovarian cancer patients who had developed resistance to PARP inhibitor therapy. These patients all suffered with ovarian cancer positive for *BRCA* mutations. Preclinical data has previously suggested that exposure to PARP inhibitors may reduce the efficacy of subsequent conventional chemotherapy in woman with *BRCA1/2* mutation carrier ovarian cancer, particularly impacting the success of platinum agents.

The study monitored the progress of 89 individuals with *BRCA*-mutated ovarian cancer at centers worldwide. All these individuals received chemotherapy after they ceased responding to PARP inhibitor therapy with an agent termed olaparib. Upon analysis it was established that approximately half of the olaparib-resistant patients demonstrated a significant decrease in tumor burden when treated with subsequent platinum-based chemotherapy. The results indicate that women previously heavily pretreated with PARP inhibitors still maintain the potential to respond to other chemotherapy agents, thus indicating that patients could live longer if they receive both therapies.

Genetic analysis using genome sequencing was also employed to try to determine the genetic mechanisms responsible for the development of resistance to PARP inhibitors in ovarian cancer. Previously, it has been believed that this resistance was established via the acquisition of further mutations in the *BRCA* genes. However, in six of the individuals involved in the study no further *BRCA* mutations were identified, suggesting that resistance to therapy can also be developed in alternative ways.

The authors conclude that their findings support further development of the use of PARP inhibitors in ovarian cancers that harbor *BRCA* mutations. "Our study finds that for many women with ovarian cancer, it is not a case of either/or chemotherapy or PARP inhibitors – there is a good chance that they may respond to both. Although some scientists were concerned that using PARP inhibitors would prevent chemotherapy from being effective, we've resolved that concern by showing that both drug types can work in the same patients," concluded Kaye.

– Written by Emily Brown

Sources: Ang JE, Gourley C, Powell CB *et al.* Efficacy of chemotherapy in BRCA1/2 mutation carrier ovarian cancer in the setting of PARP inhibitor resistance: a multi-institutional study. *Clin. Cancer Res.* 19, 5485–5493 (2013); The Institute of Cancer Research press release: www.icr.ac.uk/press/press_archive/press_releases_2013/24078.shtml

ISSN 2041-6792
10.4155/CLI.13.117

Vaccine potentially offers children up to 18 months of malaria protection

A large-scale, Phase III trial has demonstrated that the malaria vaccine candidate RTS,S is able to protect young children from clinical malaria for up to 18 months post-vaccination. Researchers analyzed the efficacy of RTS,S in addition to its public health impact in the context of malaria control measures that already exist and are used by a number of the trial participants. The outcomes of this study were presented at the *Multilateral Initiative on Malaria Pan African Conference* (Durban, South Africa).

These results indicate that over a follow-up period of 18 months, children aged between 5–17 months old at first RTS,S vaccination experienced 46% fewer clinical malaria cases as compared with those who were given a control vaccine. In the GlaxoSmithKline (Brentford, UK) press release, it is stated, "An average of 941 cases of clinical malaria were prevented over 18 months of follow-up for every 1000 children vaccinated in this age group, noting that a child can contract more than one case of malaria." In addition, there was a 36% reduction in severe cases of malaria and a 42% reduction in malaria hospitalizations.

In addition to the aforementioned cases in children, at first vaccination with RTS,S, infants aged between 6–12 weeks old experienced 27% fewer cases of clinical malaria. A total of 444 clinical malaria cases were prevented per 1000 vaccinated infants over an 18 month follow-up period.

The efficacy of the vaccination was also separately investigated at each trial site, representing a broad range of malaria transmission settings. In these assessments, it was demonstrated that efficacy was statistically significant at all sites in young children and four sites in infants.

Over time, the efficacy of the vaccine declined. Previous outcomes from a 1-year follow-up of the Phase III trial demonstrated that, for the 5–17 month old children, the RTS,S efficacy was 56% against clinical malaria and 47% against severe malaria. Furthermore, in the 6–12 week old infants, the efficacy was 31% against clinical malaria and 37% against severe malaria.

Taken together, this study indicates that at first RTS,S vaccination, the number of malaria cases in 5–17 month old children almost halved over an 18-month follow-up period. Furthermore, first vaccination appeared to reduce malaria cases in 6–12 week old infants by approximately one-quarter. In 2014, it is expected that data from 32 months of follow-up, in addition to the impact of a 'booster' dose given 18 months after the first three doses, will be made available. Andrew Witty (GlaxoSmithKline) states, "These data support our decision to submit a regulatory application for the vaccine candidate which, if successful, would bring us a step closer to having an additional tool to fight this deadly disease."

– Written by Hannah Branch

Source: GlaxoSmithKline press release: Malaria vaccine candidate reduces disease over 18 months of follow-up in late-stage study of more than 15,000 infants and young children: www.gsk.com/media/press-releases/2013/malaria-vaccine-candidate-reduces-disease-over-18-months-of-foll.html

Adjuvant gemcitabine appears to offer survival benefit in resected pancreatic cancer

Pancreatic cancer is associated with a poor prognosis, owing in part to our inability to detect the disease at an early stage and its poor sensitivity to established chemotherapy and radiotherapy treatment regimens. Where possible, surgical resection with curative intent is carried out in patients suffering from pancreatic cancer; however, there is no current consensus regarding the use of addition treatment after surgery. Currently, the majority of patients who undergo initial treatment will relapse within two years and the 5-year survival rate for the disease is <25%. Gemcitabine is the standard therapy used in patients suffering from advanced pancreatic cancer, yet no survival benefit of its use in the adjuvant setting has previously been demonstrated.

Helmut Oettle of the Charite-Universitatsmedizin Berlin (Berlin, Germany) and colleagues have recently conducted a follow-up of a randomized trial that previously compared pancreatic cancer patients treated with 6 months of adjuvant gemcitabine with those who underwent observation alone after surgery. Their intention was to determine whether gemcitabine therapy conferred any improvement in overall survival to these patients. The results of their analysis were published last week.

Patients were recruited to the trial from July 1998 to December 2004, with follow-up continuing through until September 2012. These patients had all undergone complete macroscopic removal of pancreatic cancer. A total of 368 patients. 354 of whom were eligible for treatment. were randomized to either an observation group or a treatment group. At the cessation of follow-up, 308 (or 87%) of these individuals had relapsed and 316 (89.3%) individuals had died of the disease. Of those still alive 23 had been part of the treatment arm of the study, having received gemcitabine treatment, and 15 had been in the observation group.

Further analysis of the data indicated that the median disease-free survival was 13.4 months in the treatment group, compared with 6.7 months in the observation group. Overall survival was calculated at a median of 22.8 months in the gemcitabine arm and 20.2 months in the observation arm, a statistically significant difference. Gemcitabine appeared to grant a 10.3%

improvement in 5-year overall survival and a 4.5% increase in 10-year survival when compared with observation alone.

It is concluded in the article that, "[These] data show that among patients with macroscopic complete removal of pancreatic cancer, the use of adjuvant gemcitabine for 6 months compared with observation resulted in increased overall survival as well as disease-free survival. These findings support the use of gemcitabine in this setting."

– Written by Emily Brown

Sources: Oettle H, Neuhaus P, Hochhaus A *et al.* Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer. *JAMA* 310(14), 1473–1481 (2013); JAMA Network press release: http://jama.jamanetwork.com/article.aspx?articleid=1750131

Trial demonstrates radiotherapy to be as effective as surgery in bladder cancer

Removing the bladder is the standard treatment for aggressive bladder cancer, but this can result in severe side effects. A Cancer Research UK study has demonstrated the minimal side effects and effective disease control that two radiotherapy approaches can provide for patients with aggressive bladder cancer.

Researchers at the University of Birmingham (Birmingham, UK) and the Institute of Cancer Research (London, UK) led the BC2001 radiotherapy study, which compares radiotherapy to the whole bladder with that targeted to the tumor itself. The current study aimed to investigate the efficacy of these two different radiotherapy approaches and included a 5-year follow-up to determine survival rates and tumor recurrence.

The two techniques studied were seen to prevent tumor recurrence in over 60% of patients for at least 2 years, and in those patients whose disease did return, it was demonstrated to be less aggressive and only required local treatment. After 5 years, survival rates for both radiotherapeuptic strategies were comparable to those for patients who underwent surgery to remove the bladder (approximately 40%). However, the study also demonstrated that those who received either type of radiotherapy were at a much lower risk of experiencing severe side effects.

Robert Huddart, lead investigator states, "Our study was part of the largest ever clinical trial of radiotherapy in bladder cancer and shows that patients with the disease can be treated effectively with radiotherapy. With similar success rates to surgery and fewer side effects, whilst allowing patients to retain a functioning bladder, radiotherapy should be seen as an alternative to surgery. The introduction of image-guided radiotherapy and more sophisticated ways of giving radiotherapy will hopefully further reduce any side effects that patients experience."

Kate Law, Director of clinical research at Cancer Research UK, commented, "Many thousands of patients take part in Cancer Research UK-funded clinical trials every year, and it's only by carrying out studies like this that we can test different approaches to find the most effective and safest treatments."

– Written by Elizabeth Webb

Sources: Cancer Research UK Press Release: www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2013–10–01-radiotherapy-bladder-cancer; Haddart RA, Hall E, Hussain SA *et al.* Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 Trial (CRUK/01/004). *Int. J. Radiat. Oncol. Biol. Phys.* 87(2), 261–269 (2013).

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