towards a more personalised therapeutic approach for patients with chronic lymphocytic leukaemia. Further research in this field, preferably a large prospective, randomised trial (as also suggested by the authors of the study), would be highly beneficial in order to validate the abovementioned promising findings.

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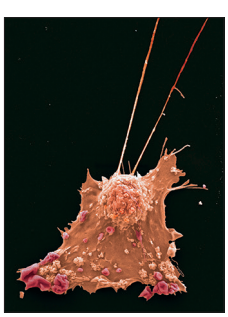
CDK4/6 inhibitors in breast cancer: a role in triple-negative disease?

Pharmacological inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) were developed on the premise that they would inhibit the proliferation of cancer cells by arresting them in the G1 phase of the cell cycle.[1] Consistent with this idea, CDK4/6 inhibitors have proven to be highly efficacious in the treatment of metastatic hormone receptor-positive breast cancers, most of which depend on the cyclin D-CDK4/6–retinoblastoma protein axis for sustained cancer cell proliferation.[2,3] By contrast, the use of CDK4/6 inhibitors in triple-negative breast cancers, a group of tumours that frequently shows genomic or functional loss of retinoblastoma protein has received considerably less enthusiasm.[4]

In this context, Antoinette Tan and colleagues' Article in *The Lancet Oncology* is intriguing.[5] The authors enrolled patients with metastatic triple-negative breast cancer to a three-arm, randomised, phase 2 trial. Patients in the control group (group 1) received conventional chemotherapy (intravenous carboplatin and gemcitabine), and those in the two experimental groups received the same chemotherapy plus trilaciclib (a selective, intravenously administered CDK4/6 inhibitor), given either as a single dose before each chemotherapy infusion (group 2) or on the day before and day of each chemotherapy infusion (group 3). Surprisingly, overall survival for patients in the trilaciclib groups was significantly longer than for those in the control group.

Before unpacking the results of this trial, we must understand the rationale for undertaking it in the first place. This understanding is especially important because of concerns that by inducing G1 arrest in tumour cells CDK4/6 inhibitors can antagonise the effect of chemotherapies that typically exert their effects in the S, G2, or M phases. The investigators of this study did not appear to deem this effect to be a problem for this particular trial, presumably because of the high frequency of functional retinoblastoma protein deficiency in triple-negative breast cancers; instead, their intention was to take advantage of this antagonism in haemopoietic cells—inducing G1 arrest in bone marrow progenitors to protect them from the cytotoxic effects of chemotherapy. Indeed, the primary objective of the trial was actually to determine whether trilaciclib reduced chemotherapy-related neutropoenia. The concept is supported by previous observations that trilaciclib induces G1 arrest in haemopoietic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stem cells and myeloid progenitor cells within 4 h of administration, rendering them less vulnerable to chemotherapy-induced apoptosis in both mice and humans.[6] Furthermore, the authors hypothesised that amelioration of haematological toxicity by trilaciclib might improve survival by reducing chemotherapy dose reductions or delays, or both.

The trial did not meet its primary objective, because trilaciclib did not reduce either the occurrence or duration of severe neutropoenia. Severe neutropenia occurred in nine (26%) of 34 patients in group 1, 12 (36%) of 33 patients in group 2, and eight (23%) of 35 patients in group 3 (p=0·70). Mean duration of severe neutropenia was 0·8 day (SD 2·4) in group 1, 1·5 days (3·5) in group 2, and 1·0 day (2·6) in group 3 (group 3 *vs* group 1 one-sided adjusted p=0·70). If anything, the number of patients requiring chemotherapy dose reductions or discontinuation due to neutropoenia was numerically higher in the two trilaciclib groups; yet despite this fact, patients in the trilaciclib groups had a longer progression-free survival (median 9·4 months [95% CI 6·1–13·0] in group 2 and 7·3 months [6·2–12·9] in group 3 *vs* 5·7 [3·4–9·2] months in group 1) and overall survival was significantly longer than those in the control group (median 20·1 months [95% CI 10·2–not reached] in group 2 and 17·8 months [12·9–not reached] in group 3 *vs* 12·6 months [6·3–15·6] in group 1; group 3 *vs* group 1 two-sided p=0·0023). This result is both remarkable and perplexing, and begs the question: why would intermittent administration of a CDK4/6 inhibitor with chemotherapy improve overall survival for patients with metastatic triple-negative breast cancer? One possibility is that the result is simply an artifact of this particular study, which is substantially limited by its size (only 33–35 patients per group), the lack of masking, and the relative immaturity of the overall survival data analysed. Furthermore, the sizeable improvements in overall survival were not accompanied by large improvements in progression-free survival or the proportion of patients who had an objective response, rendering them more difficult to reconcile.

Despite these limitations, the results remain fascinating because a biological hypothesis exists that could also explain the overall survival improvement—namely, the enhancement of antitumour immunity by trilaciclib. CDK4/6 inhibitors, including trilaciclib, have been shown to enhance antitumour immune responses through several mechanisms including the direct stimulation of T-cell effector function and a preferential suppression of regulatory T-cell proliferation.[7,8] Furthermore, by only administering trilaciclib just before chemotherapy infusions, prevention of chemotherapy-induced T-cell apoptosis and bone marrow myeloid skewing (both immunosuppressive occurrences) might be possible while preserving intra-tumoural cytotoxic T-cell proliferation.[6,7,9] Finally, a slight increase in progression-free survival indicating improvement in overall survival, as was seen in this study, has been observed with other immune-activating treatments in breast cancer, further hinting that immune mechanisms might be in play.

It is not yet known why trilaciclib improved overall survival in this study or whether the result will be validated. As a first step, a larger blinded trial should be undertaken as a matter of priority. In parallel, researchers must continue their efforts to elucidate the unanticipated effects of CDK4/6 inhibitors on antitumour immune responses; the results of this trial will certainly go a long way towards motivating them in their pursuits.

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Hyperbaric oxygen for radiation cystitis

Delayed cystitis secondary to therapeutic radiation is an uncommon but serious complication that, in its most serious expression, is likely to require multiple serial blood transfusions and can even be lethal. Treatment with chemical and electrocautery is frequently employed but the cystitis is subject to frequent recurrence. In *The Lancet Oncology*, Nicklas Oscarsson and colleagues[1] present the results of a randomised, controlled trial reporting the effects of hyperbaric oxygen therapy in the treatment of moderately severe radiation-induced cystitis. This work is the culmination of years of effort in recruiting patients by five Nordic university medical centres to this well-designed and very important trial. Eventually, and not including patients who withdrew immediately after randomisation, 41 patients assigned to hyperbaric oxygen therapy and 38 controls were available for intention-to-treat analysis. All but one patient in the intervention group completed their course of hyperbaric oxygen, consisting of 30–40 daily treatments at 240–250 kPa for 80–90 min of 100% oxygen at pressure. Patients in the control group received standard care, the nature of which was not specified in the study report. Primary outcome measures consisted of self-assessed urinary symptoms before and 4–6 months after therapy assessed with the Extended Prostate Index Composite (EPIC) score, and general health-related quality of life assessed with 36-item Short Form (SF-36) questionnaire. Additionally, cystoscopies were done before and after the intervention, with findings from the gross bladder mucosa assessed by urologists masked to treatment assignment and compared with the Radiation Therapy Oncology Group's Morbidity Grading System. Biopsies of the bladder mucosa were also taken to be analysed and reported later.

At follow-up, self-assessed urinary symptoms and health-related quality of life (general health on the SF-36) and the gross morphological grading of bladder mucosa, were significantly different in favour of the intervention group. The hyperbaric oxygen therapy group improved by a mean of 17·8 points on the 100-point EPIC urinary total scale compared with a mean improvement of only 7·7 points in the control group (difference between group means 10·1 points [95% CI 2·2–18·1], p=0·013). Although not a part of the original study design, patients in the intervention and control groups who were also affected by radiation proctitis had their EPIC bowel scores compared before and after treatment. This analysis also showed significantly improved results in the hyperbaric oxygen therapy group compared with the control group.

The investigators state that their study design was inclusive but also pragmatic. They discuss the potential criticism that their design was not masked except for the gross morphometric assessment of the bladder. They note that other hyperbaric oxygen therapy trials have been masked, but at least some have been affected by poor recruitment, and all have required extensive commitment of scarce resources. Certainly, the placebo effect is well known. However, in these patients who had been affected by radiation-induced cystitis for several years, in delaying the assessment of the primary outcome for 4–6 months after hyperbaric treatment, any placebo effect would likely have faded from the patient's mind. A Cochrane analysis[2] of placebo-controlled trials shows that perception—and not physiological improvement—is at the heart of the placebo effect.[2] Another potential criticism is that patients in the control group were allowed to cross over after the primary outcome assessment at 6–8 months after randomisation, and nearly all did so. Recall again that these patients had had symptoms for approximately 3 years on average and the natural history of this disorder had already been well established. Chong and colleagues[3] have

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