instead be invested in smarter clinical trial designs that can answer relevant clinical questions, such as whether sequencing of drugs is better than combination therapies, or defining the optimal duration of adjuvant treatment. One advantage of having so many different therapeutic options available from different pharmaceutical companies is that the possibilities for conducting such truly necessary clinical trials multiply. Fortunately, an embarrassment of riches.

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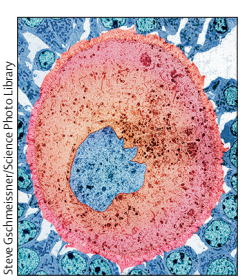
Another step towards improving oncofertility counselling of young women with Hodgkin's lymphoma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Possible chemotherapy-induced premature ovarian insufficiency is of great concern for female premenopausal patients with cancer. Therefore, appropriate counselling on the risk of premature ovarian insufficiency is now mandatory in all countries.[1,2] Oncofertility counselling is of particular importance for women who have Hodgkin's lymphoma, who are often diagnosed at a young age. However, the counselling of these women can be quite complex because of the paucity of accurate data to estimate the effect of different chemotherapy regimens on their gonadal function. Previous studies in this setting were mostly retrospective or relied only on menstrual function after treatment to define premature ovarian insufficiency, a measure that is not an optimal surrogate for assessing gonadal damage associated with treatment.

In *The Lancet Oncology*, Richard A Anderson and colleagues[3] report important results for helping physicians informing premenopausal women with advanced Hodgkin's lymphoma about the risk of chemotherapy-induced premature ovarian insufficiency associated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or AVD, or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) chemotherapy.[3] In this substudy, done within the RATHL trial (NCT00678327), biomarkers of ovarian function during and up to 3 years after chemotherapy were assessed in women younger than 45 years at the time of diagnosis. Specifically, 67 participants were monitored for serum antimüllerian hormone concentrations and 321 participants for follicle-stimulating hormone concentrations

Despite a few limitations, including the small sample size of the antimüllerian hormone analysis, particularly of those who were treated with BEACOPP, and the lack of collection of participant information from the main RATHL cohort that could have had a potential effect on outcomes (eg, use of hormonal contraceptives, previous fertility preservation procedures, and menstrual status after chemotherapy), this study provides more precise information than previous reports to counsel women with Hodgkin's lymphoma on gonadal damage induced by ABVD, AVD, or BEACOPP. The results from this study raise several factors for consideration by patients and physicians.

First, the study confirms that both the type of chemotherapy and patient's age at the time of treatment remain the two major determinants of risk of premature ovarian insufficiency for all patients with cancer.[4,5] Antimüllerian hormone concentrations decreased substantially during both chemotherapy regimens; however, while antimüllerian hormone

concentrations recovered to before treatment levels in those patients given ABVD or AVD by 1 year after treatment, little recovery of antimüllerian hormone concentrations was seen after treatment with BEACOPP.[3] In Anderson and colleagues' study, age was shown to be a crucial factor, with increased risk of chemotherapy-induced premature ovarian insufficiency after both regimens in women aged 35 years and older at the time of diagnosis.

Second, these results highlight the need for a standardised definition of premature ovarian insufficiency. Different endpoints (menstrual function only, ovarian biomarkers only—as in the present study—or a combination of the two) and timing of its assessment (ranging from a few months up to several years after chemotherapy) have been used to define chemotherapy-induced premature ovarian insufficiency. Therefore, cross-study comparisons remain difficult, even when the same chemotherapy regimens have been assessed. Guidelines suggest use of a composite endpoint that includes both amenorrhoea and a hormone profile after menopause,[6,7] and assessing chemotherapy-induced premature ovarian insufficiency at least 2 years after the end of treatment.[7] In the present study, recovery of ovarian function, as measured by follicle-stimulating hormone concentrations, occurred by 1 year after the end of treatment for most patients (75% treated with ABVD or AVD and 33% treated with BEACOPP), but recovery can also happen during the second year (18% of participants treated with ABVD or AVD and 50% with BEACOPP) with little chance of recovery thereafter. These results support the expert opinion-based indication to assess ovarian function after chemotherapy no earlier than 2 years after treatment completion.[7]

Third, although this study provides further evidence on the role of antimüllerian hormone as a biomarker of gonadotoxicity, the clinical utility of its assessment during treatment and subsequent follow-up remains to be fully determined. As shown in other studies,[8,9] both resumption of menstrual function and spontaneous conception can be observed in women with low concentrations of antimüllerian hormone.[8,9] Similarly, in Anderson and colleagues' study,[3] some pregnancies were observed in women with very low antimüllerian hormone levels. Hence, the best predictor of infertility in cancer survivors remains to be identified.

Finally, this study raises the crucial issue of discussing the possibility of reducing the risk of premature ovarian insufficiency.[1,2] Preservation of ovarian function (ie, reducing the risk of chemotherapy-induced premature ovarian insufficiency) should be distinguished from preservation of fertility (ie, improving the chances of pregnancy after treatment) and can be considered of important value also by women without childbearing desire. While cryopreservation of gametes is the first option to preserve fertility, the use of temporary ovarian suppression with gonadotropin-releasing hormone agonists during chemotherapy can now be offered for ovarian function preservation in patients with breast cancer, but its efficacy has not yet been shown in patients with Hodgkin's lymphoma.[9,10] The results of Anderson and colleagues' study highlight the importance of discussing access to these options in women older than 35 years, irrespective of chemotherapy type, and among candidates to the BEACOPP regimen, irrespective of their age. Very young women undergoing ABVD or AVD chemotherapy probably do not need to access these options, but they could be proposed later in life if additional treatments are required.

Results from the ovarian function biomarker analysis ongoing within the AHL 2011 trial (NCT01358747) are awaited to provide further evidence on the gonadotoxicity of BEACOPP chemotherapy in premenopausal women with Hodgkin's lymphoma.

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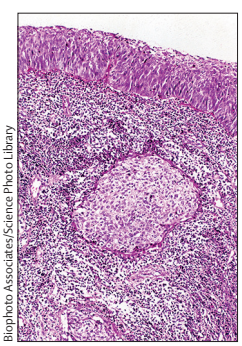
Camrelizumab for nasopharyngeal carcinoma: a new hope?



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Wenfeng Fang and colleagues[1] report on two phase 1 studies of the programmed cell death-1 (PD-1) inhibitor, camrelizumab (SHR-1210), as a treatment for patients with recurrent or metastatic nasopharyngeal carcinoma. The first trial tested camrelizumab monotherapy in 93 patients who received at least one previous line of treatment for recurrent or metastatic nasopharyngeal carcinoma. The second trial tested camrelizumab in combination with gemcitabine and cisplatin as a first-line treatment in 23 treatment-naive patients with the same diagnosis. Both trials showed good safety profiles with no treatment-related deaths observed in patients treated with camrelizumab monotherapy or camrelizumab combined with chemotherapy. The more interesting findings are the preliminary antitumor activity of camrelizumab in both settings: 31 (34%; 95% CI 24–44) of 91 patients who received previous treatment achieved an overall response with camrelizumab monotherapy (two patients had a complete response) and 20 (91%; 77–97) of 22 patients with the combination of camrelizumab and chemotherapy as first-line treatment (one patient had a complete response). These results are the most promising so far reported for PD-1 inhibitors tested in nasopharyngeal carcinoma.

Two previous studies reported on the preliminary antitumor activities of PD-1 inhibitors in patients with previously treated recurrent or metastatic nasopharyngeal carcinoma. The KEYNOTE-028 study[2] showed that seven (26%; 95% CI 11·1–46·3) of 27 patients with previously treated, advanced disease achieved an objective response with pembrolizumab. The NCI-9741 trial[3] showed that nine (20·5%; 95% CI 9·8–35·3; one complete repsonse) of 44 patients with previously treated recurrent or metastatic nasopharyngeal carcinoma achieved an objective response with nivolumab. Further investigation of the underlying cause of the differences in activity (objective responses) reported in these three studies would be of interest. The difference might be due to the activity of each drug, but the mechanism of action appears very similar for different PD-1 inhibitors. Variations in patient populations, tumour biology, and previous treatments received might be also important especially for small patient cohorts. Both KEYNOTE-028 and NCI-9741 are international studies including 63% and 82·2% Asian patients, respectively; whereas the current study by Fang and colleagues[1] was done in an endemic Chinese population. The proportion of WHO type 2 or 3 tumours in KEYNOTE-028 was 66·7%, 82·2% in NCI-9742, and 82% in the camrelizumab monotherapy trial of the current study. In terms of patient selection, KEYNOTE-028 only included patients with programmed cell death ligand-1 (PD-L1)-positive tumours, whereas both NCI-9742 and the current study enrolled patients with unselected histologies. In NCI-9742, 40% of patients had PD-L1-positive tumours, which was associated with an improved response (six [33%] of 18 patients) compared with PD-L1-negative tumours (three [13%] of 23 patients). PD-L1 positivity also appears to be predictive of response to PD-1 inhibitors in other head and neck squamous cell carcinomas.[4,5] PD-L1 status was not reported by Fang and colleagues in the current study. Thus, the improvement in the frequency of objective responses might be affected by the proportion of patients with PD-L1-positive tumours in the study population. Interestingly, the study also found that six (75%) of eight patients who had previous treatment with ipilimumab and subsequent camrelizumab monotherapy achieved an objective response. This outcome might suggest that previous priming with ipilimumab could improve the