were in the first year, a substantial proportion of them were in the second year and a lower proportion in the third year. However, the exposure-adjusted rate of pneumonitis appeared to be nearly stable (while infrequent) over the first 3 years of exposure. Although the CheckMate trials found few treatment-related adverse events occurring after the third year of exposure, the KEYNOTE-001 study reported that they might still occur, albeit rarely, between years 3 and 5. These results strongly suggest that patients should be monitored for—and their treating physicians should be acutely conscious of—treatment-related adverse events for the entire duration of exposure. However, unlike chemotherapy, there does not appear to be any cumulative toxicity with immunotherapy.

A remaining question is the optimal duration of immune checkpoint inhibitor treatment for patients with objective response. Should treatment be continued until progression or toxicities are seen? Should treatment be stopped in case of a prolonged objective response? Several trials, including IFCT-1701 DICIPLE (NCT03469960), are currently underway to offer answers to these questions.

Now that a combination of chemotherapy and immunotherapy is becoming the standard first-line treatment for all histologies and for all PD-L1 statuses, it is reasonable to expect greatly improved outcomes with an increasing proportion of patients alive 5 years after diagnosis. The horizon might still be far, but it appears that the tide has turned.

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P-JS and SC report grants, board membership, and financial support for congress from AstraZeneca, Bristol-Myers Squibb, and Roche. P-JS also reports grants and board membership from Merck Sharpe and Dohme. SC also reports financial support for congress from Merck Sharpe and Dohme.

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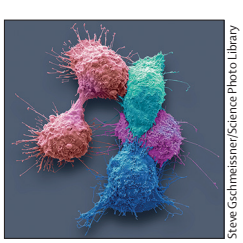
Chemotherapy-free, but not quite free chemotherapy

Seasoned health-care providers caring for women with epithelial ovarian cancer will not-so-fondly recall the days when upfront clinical trials took several years to complete and consisted of thousands of patients randomly assigned to different combinations or sequences of a handful of cytotoxic drugs with generally disappointing findings.[1] The fact that the vast majority of women will eventually relapse after treatment with primary chemotherapy, and that most of these cases will be recognised at least 6 months after completion of primary chemotherapy, is well established. This platinum-sensitive group of patients generally has a relatively good prognosis following relapse and has traditionally been treated with carboplatin in combination with another cytotoxic drug, such as paclitaxel, gemcitabine, or liposomal pegylated doxorubicin.[2,3] After that, the available options historically consisted of the same short list of cytotoxic drugs, used and reused with diminishing results. Conceptually, this period 15–20 years ago was a much simpler time, with long intervals between the emergence of any practice-changing data. One common phrase circulating at oncology conferences and congresses was that by the time the study had been completed and reported, researchers would have already moved on to more promising options. Yet,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Published Online
August 29, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30492-9

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fortunately, times are changing and research in this area of oncology is now progressing.

The AVANOVA2 trial presented by Mansoor R Mirza and colleagues[4] in *The Lancet Oncology* exemplifies just how far research in epithelial ovarian cancer has advanced. The randomised, phase 2 design required less than 100 patients and the study met its accrual goals within 1 year. Broad eligibility criteria at 15 international enrolling sites should mean that the study findings—showing that the combination of niraparib plus bevacizumab significantly improved progression-free survival compared with niraparib alone—are readily applicable to most women with platinum-sensitive relapse of ovarian cancer. The use of progression-free survival as the primary endpoint (instead of overall survival) allowed a more rapid data capture and much faster presentation and publication of the results. Quality of life measures—a very important topic, but neglected for many years—were also included, and showed no significant differences between the two treatment groups and no clinically meaningful changes in quality of life over time.[4] The trial also emphasises the shift in treatment approach away from traditional cytotoxic chemotherapy towards newer, more patient-friendly agents, with fewer side-effects. All of this translates into a win–win scenario for patients, but what should the typical clinician take away from this? How will this study affect their decision making when the next patient comes through the door?

My guess is that the niraparib and bevacizumab combination will be a novel, but largely unproven, treatment option in an ever-expanding list of choices. It will be unproven in the sense that it has not been directly compared with the gold standard of platinum-based therapy. The shortcomings are well described by the investigators, to include the open-label design and lack of blinded independent review of progression-free survival, leading to potential observer bias. Certainly future trials of this combination could lead to a new treatment strategy (or not), but the real question is where does this fit in clinical practice, now? And where will it fall to when the randomised phase 2–3 trial of olaparib with or without cediranib (NCT02502266) is published? This too is a chemotherapy-free dosing schedule tested in the same population, with the added advantage of both drugs being oral agents. More options, few of which have been directly compared with each other, will add to the confusion of decisions regarding the most beneficial therapy in this setting.

The molecular mechanisms of epithelial ovarian cancer cannot yet be tested and used to consistently direct personalised therapy. Mirza and colleagues did homologous recombination deficiency testing on archival samples (ie, the original tumour) that were largely unrevealing, but no other translational study endpoints were followed.[4] Such translational studies add to the expense, the complexity, and the workload of doing a trial, many of which are designed and patients randomised entirely on the basis of clinical features. The consequence of this study, unfortunately, is that we as researchers are no closer to being able to target individualised treatment in this population.

One sensitive and unpopular topic that is rarely discussed is cost. I am unaware as to how much prescribing the niraparib and bevacizumab combination at my institution would cost, but I am confident it would be expensive. Should this matter in clinical decision-making? How would the typical clinician even obtain a reasonably accurate expense estimate? To some extent, this issue would matter a great deal to the patient who might be exhausting their financial resources.[5]

Mirza and colleagues are to be congratulated on their high-quality, efficient study design, as well as their clear presentation of findings that will unquestionably resonate with clinicians caring for these patients. Excellent trials should lead to more questions and I would put AVANOVA2 in this category. Fortunately, continued advances in clinical trial development will lead to quicker answers and faster progress in fine-tuning our therapeutic choices for relapsed platinum-sensitive ovarian cancer.

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I report honoraria from AstraZeneca.

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Solid organ transplantations in childhood cancer survivors: an unrealised research potential

Do anti-cancer and immunosuppressive agents cause cancer in man? What is the effect of these agents on existing cancers? These key fundamental questions were raised in 1972 by Penn and Starzl in their article entitled 'The effect of immunosuppression on cancer'.[1] Resulting speculations, which are highly relevant for the topic of solid organ transplantation in childhood cancer survivors, are considered by Andrew C Dietz and colleagues[2] in *The Lancet Oncology*.

With the advent of multimodal therapy, survival from childhood cancer has improved over the past 50 years, now reaching more than 80% at 5 years after diagnosis in developed European countries.[3] However, treatments are harsh and might cause serious adverse effects later in life.[4] High-dose irradiation and exposures to chemotherapeutic drugs might lead to treatment-induced end-organ failure and consequently the need for organ transplantation. To prevent rejection of organ transplants, post-transplant immunosuppressants are used, which might lead to additional adverse outcomes.

The question raised in 1972 concerning the role of immunosuppressants for facilitating tumour development is still an ongoing concern, and one of the most severe long-term complications of immunosuppression in the transplant population is de novo malignancies. In the particular case of cancer survivors undergoing transplantation, the occurrence of immunotherapy-associated relapse of the primary cancer or development of secondary malignancies is of great concern as this population have already proved the potential to develop cancers. Several studies have reported that pre-transplant malignancy in adult patients with cancer is associated with an increased risk of developing de novo malignancies after solid organ transplantation compared with those without malignancies.[5] Yet, the magnitude of this problem in childhood cancer survivors undergoing solid organ transplants is still to be assessed.

Similar to other transplant candidates, childhood cancer survivors undergo a thorough evaluation process before transplantation and survivors must be in tumour remission for some time, depending on the type of cancer, before being considered for transplantation.[6] Very limited evidence is available to guide decision making on whether and when the childhood cancer survivor should undergo transplant surgery. So far, the decision seems to be based on extrapolations from the evidence obtained in adult patients with cancer, which might not be appropriate.

In *The Lancet Oncology*, Dietz and colleagues[2] provide new insight into this field. Using the unique resources within the Childhood Cancer Survivor Study (CCSS), the authors provide novel data on kidney, heart, liver, and lung transplantations in childhood cancer survivors—an area to date only touched upon in case reports and small case series. Aimed at defining the incidence of, risk factors for, and survival after end-organ failure and transplantation, a retrospective cohort of 13 318 5-year survivors of childhood cancer diagnosed between 1970 and 1986 below age 21 years were linked to a database of US organ transplants revealing that 100 CCSS participants went on to receive 103 transplants later in life, with an additional 67 survivors being placed on the waiting list for an organ. Organ-specific radiation and chemotherapy exposures were shown to increase the risk of requiring solid organ transplantations following cure of childhood cancer. Furthermore, post-transplant survival outcomes showed that an organ transplant should be considered for 5-year survivors with life-threatening end-organ failure.

Spencer Grant/Science Photo Library

Published **Online**
August 27, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30499-1

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