

Let's return to the "belly bath"

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For the greater part of its natural history, ovarian cancer is a disease confined to the abdominal cavity. Hence, the attractiveness of intraperitoneal chemotherapy (IPC), which has now been shown to delay progression and improve survival in patients with stage III disease with minimal residual tumor.¹ It has been suggested by the US National Cancer Institute, and by many reviewers of this article, that IPC should now be considered as a standard treatment for these patients. All reviewers have commented on the logistical difficulties and expressed their surprise that these good results were achieved while only 42% of patients on the IPC arm completed the treatment. All have commented on the increased toxicity, relating it to the 'continuous infusion effect' as intraperitoneal drugs, left in the abdominal cavity in perpetuity, are slowly absorbed. All have missed the major point.

The definitive work on the pharmacokinetics of intraperitoneal drug administration was reported by Dedrick *et al.*,² in a paper that was one of the most cited in the English literature. The dose advantage of IPC treatment was clearly shown, as the absorption of most drugs via the peritoneum is slow, allowing very high concentrations compared with those achieved by the intravenous route. What this study also showed, using Hypaque® (Winthrop-Stearns Inc., New York, NY) and CT imaging, was that, unless large volumes of fluid were administered, complete distribution to the interstices of the peritoneal cavity—areas freely open to access by ovarian cancer cells—was not achieved. This group followed with three landmark clinical studies using dialysis techniques to achieve a high volume of distribution, with removal of administered fluid after 2–4 hour dwell times.^{3–5} They dubbed this approach "belly bath", which indeed is what it was.

This approach exposed the entire peritoneum to high concentration of drugs using dialysis techniques, something the static infusion of 2 liters of fluid cannot do. Removing the fluid

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after a dwell time sufficient to assure tumor cell kill prevented absorption and the consequent systemic toxicity. But then the 'convenience factor' took center stage, as it often does in clinical medicine. It was said that it was too much trouble for patients to use this approach, and for 28 years IPC languished as investigators opted for bolus intraperitoneal administration of 2 liters of fluid with the naive assumption this would assure complete intraperitoneal distribution. Not surprisingly, a lot of studies showed unimpressive results. Not surprisingly, leaving a catheter in for weeks or months proved difficult for the patients, if easier for doctors and, not surprisingly, the continuous infusion effect squandered the advantage of the intraperitoneal route for avoiding systemic toxicity. What is surprising is that it worked at all, since there were tumor cells not exposed to drug with the bolus treatment. The explanation for the good results, despite that fact that only 42% of patients completed intraperitoneal treatment, is that, when it works, probably only a few intraperitoneal exposures of tumor cells to very high drug concentrations are sufficient to kill exposed ovarian cancer cells. Dr Runowitz rightly states in the Practice Point in this issue that if physicians use this approach, they should not deviate from the original published method.⁶ That is generally good advice. Would that others, who shifted from the "belly bath" to intraperitoneal bolus therapy, had done the same.

While practitioners attempt to apply IPC, it is time to study IPC as it was originally designed now that it has been shown to be beneficial. With the current drugs, coupled with intravenous treatment, one or two dialyses might well prove less toxic and more effective than bolus therapy, and might even do more than prolong survival. It might cure these patients.

VT DeVita, Jr is Editor-in-Chief of Nature Clinical Practice Oncology.

Competing interests

VT DeVita, Jr is the senior author on most of the papers cited in this article.

www.nature.com/clinicalpractice
doi:10.1038/ncponc0568

Supplementary information in the form of a reference list is available on the *Nature Clinical Practice Oncology* website.