The role of metronomic chemotherapy in the era of cancer immunotherapy: an oncologist’s perspective

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Metronomic chemotherapy (mCTX) encompasses a set of chemotherapy (CTX) doses significantly below the conventional maximum tolerated dose (MTD) and delivered largely continually (without the prolonged drug-free breaks typical of MTD CTX). That approach was in incidental use for adult patients with end-stage solid cancers at the Queen Elizabeth Hospital in Hong Kong in the late 1960s and 1970s. Because the term “metronomic chemotherapy” had not been coined then, those regimens were known as “mild CTX.” An example is intravenous cyclophosphamide (CP) 800 mg weekly or oral CP 50 mg daily taken continuously.

In general, those regimens were better tolerated than other favourite regimens, except when the dose of intravenous CP exceeded 800 mg, resulting in a risk of vomiting. Admittedly, retrospective reviews might miss adverse events such as alopecia attributable to the side effects of prior CTX. Nevertheless, I noted a mild lymphopenia in up to 20% of patients given intravenous CP—an effect that was not felt to be significant. Moreover, low-dose CP resulted in no objective responses except for a few cases in which “static disease” was achieved. Eventually, because intravenous CP was associated with anecdotal objective responses, it became my favourite “mild CTX” for end-stage patients for several years.

For similar patients at another hospital in Hong Kong, other oral mCTX regimens were in use (etoposide 50 mg daily for 3–5 consecutive days weekly or oral vinorelbine 30 mg thrice weekly). With that regimen, I noted similar anecdotal responses as for intravenous CP. However, because etoposide and vinorelbine both cause significant marrow depression, etoposide frequency was reduced to only 2–3 consecutive days weekly, and vinorelbine, to only twice weekly; however, both doses were unchanged. Interestingly, even those less-frequent administrations were associated with nonallergenic skin rashes of unknown cause. In addition, although metronomic vinorelbine was consistently associated with the highest lymphopenia rate of all mCTX regimens I ever prescribed, that side effect was still not recognized to be significant.

Since the start of the 2000s, the mechanisms of action of mCTX regimens—that is, antiangiogenesis and immunomodulation—have been better understood. Although that recognition might well be enlightening and reassuring, clinical trials for validation could hardly be organized.

Decades ago, cross-sectional imaging for precise response documentation was either not yet available or was deemed “unworthy” for patients with end-stage disease. Moreover, clinical trials of mCTX regimens had other unique problems. Intestinal absorption rates of oral mCTX agents and pharmacokinetic correlations with drug levels in blood were desirable, but were prevented by technical and logistics constraints. Although cell-kil by direct cytotoxicity— the mTD of CTX—is prompt, the indirect cell-kil of mCTX through immunomodulation or antiangiogenesis (or both) can significantly delay response. However, the short survival period for patients with end-stage disease might not be adequate to capture that delayed response. With all those unique problems, much more effort is required to conduct more reliable dose-finding and adverse event studies. Although documentation of the true response rates with mCTX might well require trials in patients naïve to CTX, randomized trials making comparisons with targeted therapy—for example, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) or the MTD of a CTX—could be very long-awaited.

Meanwhile, in the era of cancer immunotherapy, many immune checkpoint inhibitors (ICIS)—nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, tremelimumab, and ipilimumab, for example—are already in active clinical use. However, because the response rates with ICIS monotherapy are not high, combinations with other agents for higher response rates are desired. The MTDs of CTX regimens and targeted therapies (for example, the EGFR TKIs) have been used for that purpose, but toxicities remain problematic. Because mCTX is less toxic than the MTD of CTX regimens, it is worthwhile to consider whether mCTX regimens represent feasible candidates for combination with ICIS. Although lymphopenia has often been ignored in the busy clinic, its relationship to enhanced body immunity has recently been revealed. Lymphopenia induced by medium-dose CTX was surprisingly found to be associated with enhanced antitumour immunity. Because the MTD of CTX is conceptually immunosuppressive, the feasibility of mCTX regimens as more appropriate candidates for combining with ICIS should now be explored. Already, a small study in patients with triple-negative breast cancer (TNBC) has discovered the feasibility of combining an IC (nivolumab) with various modalities of treatment including
metronomic doxorubicin, cisplatin, and oral cyclophosphamide. It is now timely to discuss the relative merits of available options for combination with ICIs.

In 2018, the U.S. Food and Drug Administration approved pembrolizumab in combination with pemetrexed–carboplatin, a conventional CTX regimen, for first-line treatment of metastatic nonsquamous non-small-cell lung cancer, regardless of the expression of PD-L1. Despite the effectiveness of the combination, significant toxicity attributable to the CTX is a significant concern, especially in older patients who might poorly tolerate such combinations. Even for younger patients, the finite number of CTX cycles deliverable could prove to be inferior to continual administration of combinations. Delayed clinical responses to ICIs are well known, and problems could arise when the finite number of mTdx CTX cycles are reached without any response being achieved. In that case, there are uncertainties about whether the cycles of CTX thus delivered have actually worked to induce a good response.

Targeted therapies—for example, EGFR TKIs—might be expected to have the advantages of both indefinite administration and a more tolerable toxicity profile. However, the initial experience with combinatory administration has been associated with unexpectedly high toxicities. Nivolumab combined with erlotinib was associated with high grade 3 toxicities. Combined osimertinib and durvalumab was associated with such a high incidence rate of interstitial lung disease that trial enrolment was terminated. The combination of gefitinib and durvalumab was also associated with unexpectedly high rates of grade 3 or 4 liver enzyme elevations, and high rates of grade 3 or 4 adverse events were also associated with the combination of atezolizumab and erlotinib. Moreover, according to Atkins and Tannir, sunitinib or pazopanib combined with nivolumab for renal cell carcinoma resulted in intolerable toxicity. The lower toxicity profile of mCTX regimens therefore suggests that they might be better candidates than targeted therapies for combination with ICIs.

Clinical outcomes of various mCTX regimens for TNBC have been compared (Table 1). Of 3 selected series involving patients with TNBC, Kummar et al., reported the lowest overall response rate of 5.6% when using low-dose oral CP 50 mg daily. Although low-dose oral CP 50 mg daily is currently the dominant prescription pattern of metronomic CP, clinical performance data (Table 1) suggest that it is less effective than the other mCTX regimens, supporting my own experience in the 1960s and 1970s favouring medium-dose CP.

Regulatory T cells are specialist lymphocytes currently considered to be closely related to tumour progression or preservation. Previously, regulatory T cells were called “suppressor T cells,” because one of their main functions appeared to be suppression of excessive autoimmune reactions. Recently, excessive production of regulatory T cells has been linked to accelerated cancer cell growth. Regulatory T cells have now become a potential oncology target. For patients with glioblastoma multiforme, Sampson et al. also reported that enhanced antitumour immunity could be achieved for patients having a sustained grade 3 lymphopenia (<500 cells/mL), but without significant neutropenia after daily medium-dose oral temozolomide (100 mg/m²) for 3 weeks of each 4-week cycle.

Most recently, in vivo studies also showed that transient lymphopenia occurring with medium-dose CP could also enhance antitumour immunity. Interestingly, much higher doses had the opposite effect. Lymphopenia was found to be associated with upregulation of a host danger-sensing mechanism. Parenteral CP given every 6 days achieved robust antitumour cytotoxicity, by reaching higher peak drug levels than low-dose oral CP could, and by cutting short the long drug-free breaks of conventional mTdx regimens. The “every 6–day” schedule of medium-dose CP (equivalent to 7.3–11.4 mg/kg in adult humans) induced robust and sustained antitumour immunity after a transient lymphopenia.

The immunogenicity of CP is often related to immunogenic cell death (ICD). Conceptually, even as intact cancer cells can evade host immunity, when they are killed by specific CTX agents, a range of host responses can ensue. The uptake of necrotic cancer cells can trigger inflammatory pathways that fuel antitumour cytotoxicity. Doxorubicin, epirubicin, mitoxantrone, and oxaliplatin are also documented to be immunogenic through ICD. They are thus known as “ICD” CTX agents—

<table>
<thead>
<tr>
<th>Reference</th>
<th>Line of treatment</th>
<th>Chemotherapy</th>
<th>Patients (n)</th>
<th>Response</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoshimoto et al., 2012</td>
<td>First or second</td>
<td>Capecitabine 828 mg/m² twice daily plus cyclophosphamide 33 mg/m² twice daily for 2 weeks every 3 weeks</td>
<td>5</td>
<td>ORR: 44.4%</td>
<td>10.7</td>
</tr>
<tr>
<td>Kummar et al., 2016</td>
<td>Second</td>
<td>Cyclophosphamide 50 mg daily</td>
<td>39</td>
<td>ORR: 5.6%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cazzaniga et al., 2017</td>
<td>Second or greater</td>
<td>Vinorelbine 40 mg 3 times weekly plus capecitabine 500 mg 3 times daily</td>
<td>28</td>
<td>53.7% for CR, PR, SD combined</td>
<td>4.7</td>
</tr>
</tbody>
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Data compiled from Cazzaniga et al. Although the series were not strictly comparable, a meaningful pattern can be appreciated. In the Yoshimoto et al. series, the best progression-free survival was associated with the earliest disease. Although the Cazzaniga et al. series contained patients with the most advanced disease, half the patients still experienced some form of response to treatment (assuming that stable disease also represents a form of disease control).

PFS = progression-free survival; ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease.
example, gemcitabine, mitomycin C, etoposide, and cisplatin—can also be combined with ICIs. Those non-ICD CTX agents use other mechanisms involving myeloid-derived suppressor cells or dendritic cells. For example, the non-ICD medium-dose metronomic CTX vinorelbine was reported to be effective for TNBC (in combination with low-dose capecitabine)6. Medium-dose metronomic vinorelbine might therefore be a promising candidate for combination with ICIS for those cancers. The ongoing phase II/III MOVIE trial of metronomic oral vinorelbine plus ICIS for advanced solid tumours (NCT03518606 at http://ClinicalTrials.gov/) seems appropriate, given that oral vinorelbine has a track record of significant lymphopenia that might be associated with enhanced antitumour immunity. On the other hand, because lymphopenia is uncommon with low-dose CTX regimens, the chances of inducing antitumour immunity might also be low12. Although such preclinical and early clinical studies are thought-provoking, manipulating the dose of mCTX to achieve the desired lymphopenia would be extremely challenging in daily practice. However, clinical studies might provide useful guidance about the appropriate dose range for mCTX regimens. Additionally, the surprisingly common immune-related adverse events seen when combining ICIS with EGFR TKIs4,5 would serve as a warning to carefully monitor immune-related adverse events in the application of novel combinations.

To summarize, advances in cancer treatment might be achieved by combining considerably less-toxic mCTX regimens with ICIS in the era of cancer immunotherapy. One bottleneck is determining the appropriate dose of mCTX for combinations. Because preclinical and early clinical studies do not appear to validate the effectiveness of low-dose mCTX, higher doses of mCTX might be preferred. Preclinical and limited clinical studies suggest better enhancement of antitumour immunity upon induction of moderate lymphopenia. And yet, in the busy clinic, manipulating the dose of mCTX for skillful induction of the desired lymphopenia is challenging. Trials of mCTX regimens are useful and serve to provide “track records” for dose levels associated with significant lymphopenia. Based on such “track records,” the most appropriate dose levels of mCTX could be adopted for best results in combination with ICIS. Moreover, the unexpectedly high toxicities demonstrated in initial trials of targeted therapy plus ICIS underscore the importance of any proposed mCTX plus ICI combinations. The safety profiles of such new combinations require meticulous documentation, including the potential for autoimmune-related adverse events. It’s a long, but potentially promising, road ahead.

CONFLICT OF INTEREST DISCLOSURES
I have read and understood Current Oncology’s policy on disclosing conflicts of interest, and I declare that I have none.

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REFERENCES