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Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 167–178

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Review Article

Metronomic therapy for gynecologic cancers

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Accepted 12 March 2012

Abstract

Systemic administration of cytotoxic drugs is the primary treatment strategy for patients with advanced cancer. The effect of cytotoxic drugs is to disrupt the DNA of the cells, rendering them unable to replicate and finally killing them; therefore, the fundamental role of a wide range of treatment regimens is typically to induce lethal toxicity in the largest possible number of cancer cells. However, these cytotoxic drugs also damage the normal cells of the host, which limits the dose of the cytotoxic drug. Thus, cancer patients are usually treated at or near the maximum tolerated dose with the implicit intent of eradicating (curing) the tumor after balancing between efficacy in tumor killing and toxicity to the host. With significantly improving patient care, most efforts are focused on the corollary, "The higher the dose, the better." However, the concept that cancer could be considered as a chronic disease and might be treated like other chronic diseases to achieve a status called tumor dormancy is gaining popularity. In addition, there has been increasing interest in putting more effort into administering cytotoxic drugs on a more continuous basis, with a much shorter break period, or none at all, and generally lower doses of various cytotoxic drugs or combinations with other newer, targeted therapies, like anti-angiogenesis agents. This practice has come to be known as metronomic chemotherapy. There is still much to be learned in this field, especially with regard to optimization of the proper drugs, dose, schedule, and tumor type applications. This review will explore recent studies that have addressed the mechanism of metronomic chemotherapy in the management of various tumors, especially gynecologic cancers.
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Keywords: antiangiogenesis agent; cytotoxic drugs; gynecologic cancer; metronomic chemotherapy

Introduction

Gynecologic oncology has advanced dramatically over the past few decades, and physicians have seen the successful application of a number of conventional cytotoxic drugs to cancer conditions diagnosed in their female patients. Among these cancers, epithelial ovarian cancer (EOC) might be one of the best examples. Advances in surgical technique, anesthesia support, and intensive postoperative care significantly

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doi:10.1016/j.tjog.2012.04.002

decrease the burden of the residual EOC [1]. However, surgery alone cannot treat diseases such as EOC successfully, even after aggressive surgical intervention, partly because of the presence of some residual tumor and partly because of the high recurrence of tumors; therefore, adjuvant postoperative chemotherapy with cytotoxic drugs is nearly always needed to attempt to gain complete clinical remission [2].

EOC was one of the first solid tumors to have a chance of being successfully controlled with cytotoxic drugs, although the disease-free interval is short [3]. The fundamental goal of cytotoxic drugs is typically to induce lethal toxicity in the largest possible number of tumor cells; therefore, most research efforts in chemotherapy are focused on discovery of agents and combinations of agents, doses, and dose schedules that maximally kill tumor cells while minimizing the toxicity to the host [4].

Although more than 80% of patients with advanced EOC receiving a combination of platinum and paclitaxel as primary chemotherapy initially responded, most of them developed resistant disease [5]. Only in rare cases, for example, choriocarcinoma and germ cell tumors of the ovary [6], cures can be achieved.

The use of drug regimens that have been designed to kill as many tumor cells as possible by treating with the maximum tolerated doses (MTDs) of these cytotoxic agents have been challenged in EOC recently, although dose-intensity strategy through intraperitoneal route has been reported in success. Moreover, side effects, such as neurotoxicity and damage to proliferating cells in healthy tissues pose serious constraints on the use of chemotherapy based on MTDs [7]. To allow these susceptible normal tissues like intestinal epithelium and bone marrow cells to heal, a drug-free break period before the next dose of chemotherapy is always scheduled [8]. This break period can be as lengthy as 3−4 weeks or more, depending on which cytotoxic drug or combinations are used. This practice not only involves the re-growth of tumor cells, but also growth of selected clones resistant to the agents [9]. Therefore, the patient's tolerance is believed to be one of the key factors in this kind chemotherapy. The minimal cure rate at a such a high price had made us reconsider the feasibility of MTD-based chemotherapy [10].

The bothersome side effects of cytotoxic chemotherapy include myelosuppression, hair loss, intestinal mucosa damage, nausea, vomiting, and mucositis, not to mention the long-term cardiac (for example, adriamycin), renal (for example, cisplatin), neurologic (for example, cisplatin, and paclitaxel), and reproductive (for example, cyclophosphamide) consequences, including premature ovarian failure [11,12]. Indeed, many of the recent pharmacological advances in cancer treatment involve growth factors and antinausea drugs, which are administered to cancer patients to minimize the severity of, or accelerate recovery from chemotherapy-induced toxicities, but such "supportive-care drugs" can significantly add to the financial burden of cancer chemotherapy, and have their own side effects [10].

To minimize the toxicity of MTD regimens and improve the anti-tumor effect, the future success of chemotherapy might be dependent on the integration of the metronomic scheduling of cytotoxic chemotherapy [10] and more targeted approaches [8]. Instead of only using short bursts of toxic MTD chemotherapy interspersed with long breaks to allow recovery from the harmful adverse events, there is now a shift in thinking towards the view that more compressed or accelerated schedules of drug administration using much smaller individual doses than the MTD would be more effective [13]. Much smaller individual doses separated by a short or very short interval not only reduce certain toxicities, but perhaps even improve the anti-tumor effects as well [14,15]. In addition, some of these dosing and/or scheduling strategies are ideally suited to combining chemotherapeutics with many of the new targeted and relatively non-toxic anticancer drugs that have been or are being developed [10].

A new strategy to administer cytotoxic cancer therapy

The term "metronomic" refers mainly to the scheduling, which consists of chronic, equally spaced, and generally low doses of single or combined chemotherapeutic drugs without extended drug-free breaks [9]. Chemotherapy is conventionally prescribed at the highest level that is tolerated by the patient, in order to provide the possibility of eradicating the cancer cells (Fig. 1). The evidence supporting this hypothesis is derived from the work of Skipper and colleagues [16], who utilized an *in vitro* cancer cell culture system to demonstrate the logarithmic tumor cell kill rate with increasing chemotherapeutic doses. Application of these findings to certain hematologic cancers, or "liquid tumors", such as leukemia or

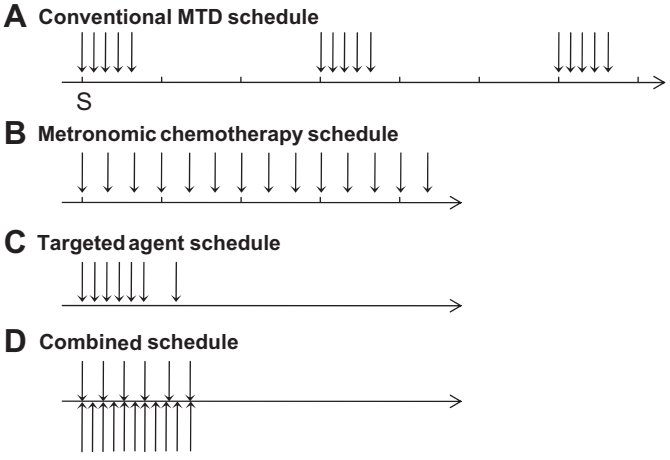

Fig. 1. Different chemotherapy regimens. Metronomic chemotherapy regimens differ from the standard MTD chemotherapy regimens that have been commonly used in medical oncology for decades. (A) In conventional chemotherapy a drug is typically given in a single bolus injection or infusion at the MTD, followed by a long break, for example, 3 weeks, before the next course of this therapy is administered; (B and C) examples of metronomic schedules are shown, in which, for example, the chemotherapy drug is administered more frequently, such as weekly (B), with no prolonged drug-free interruptions. Targeted drugs, including small molecule drugs, monoclonal antibodies, apoptosis-inducing drugs, angiogenesis inhibitors and low-dose chemotherapy, are mainly prescribed on a daily basis (C); (D) combined therapy is then ideal for the two schedules (B and C) in a chronic administration manner. MTD = maximum tolerated dose.

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