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Review

Low-dose metronomic chemotherapy: A systematic literature analysis

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Abstract Low-dose metronomic (LDM) chemotherapy, the frequent and continuous use of low doses of conventional chemotherapeutics, is an emerging alternative to conventional chemotherapy. While promising tumour control rates and excellent safety profiles have been observed, there are no definitive phase III trial results. Furthermore, the selection of patients, drug dosages and dosing intervals is empirical. To systematically review the current state of knowledge regarding LDM chemotherapy, we searched the MEDLINE, EMBASE, CENTRAL and PubMed databases for fully published LDM chemotherapy trials. We calculated the relative dose-intensity (RDI, mg/m^2/week) of each LDM regimen as compared to conventional maximum tolerated dose (MTD) dosages and the 'dosing-density' (DD, % of days with chemotherapy administration per cycle). Meta-regression was performed to examine factors associated with disease control rate (DCR; complete response (CR) + partial response (PR) + stable disease (SD)). Eighty studies involving mainly pretreated patients with advanced/metastatic breast (26.25%) and prostate (11.25%) cancers were retrieved. The most commonly used drug was cyclophosphamide (43%). LDM chemotherapy was frequently combined with other therapies (64.5%). Response rate (RR) and progression-free survival (PFS) were the most frequent primary end-points (24% and 19%). Mean RR was 26.03% (95% confidence interval (CI): 21.4–30.7), median PFS was 4.6 months (interquartile range (IQR): 2.9–7.0) and mean DCR was 56.3% (95% CI: 50.9–61.6). RDI, DD and metronomic drug used were not associated with DCR. Grade 3/4 adverse events were rare (anaemia 7.78%, fatigue 13.4%). Thus, LDM therapy appears to be clinically beneficial and safe in a broad range of tumors. However, meta-regression analysis did not identify predictive factors of response.

1. Introduction

Low-dose metronomic (LDM) chemotherapy is emerging as a novel form of chemotherapy utilization, defined as the frequent administration of conventional

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chemotherapy drugs at low doses with no prolonged drug-free breaks.[1] The term metronomic chemotherapy was originally coined in an editorial published in 2000 by Hanahan et al.[2] in which the authors comment on two pivotal preclinical studies that have laid the scientific ground for LDM chemotherapy.[3,4] Its mechanism of action is regarded as primarily anti-angiogenic in nature, affecting both the endothelial cells of tumour supplying blood vessels as well as circulating endothelial progenitor cells. In addition, recent evidence points to the presence of immunomodulatory anti-tumour activities in LDM therapy. However, the importance of such immunological and other direct anti-cancer cell effects (such as the interference with the hypoxia-induced factor 1α pathway and the targeting of cancer stem cells) remains undetermined.[5–8]

LDM chemotherapy is associated with lower treatment related toxicity than conventional maximum tolerated dose (MTD) chemotherapy.[9] This advantage is attractive in clinical practice when considering patients with residual toxicity from previous treatment or those who may not be considered fit for MTD chemotherapy, such as the elderly and frail.[10] Furthermore, the cost of a metronomic regimen may be lower than MTD chemotherapy, as a result of fewer side-effect associated expenditures and the usage of inexpensive oral drugs such as cyclophosphamide.[11]

As many phase II studies have shown the clinical benefits of LDM chemotherapy, including promising tumour control rates and excellent safety profiles,[5] its popularity continues to increase worldwide. For example, a recent survey of oncologists in Italy indicates that 72% of survey respondents have prescribed LDM chemotherapy at least once.[12] While definitive phase III trial results are pending, the usage of metronomic-like chemotherapy regimens has been shown to improve overall survival (OS) in phase III trials of early lung and breast cancer.[13,14] Currently, there are at least six randomised phase III trials in either the adjuvant setting, in patients with advanced cancer, in the elderly and frail, and as a maintenance treatment strategy following conventional induction chemotherapy [www.clinicaltrials.gov].[5,15]

Many aspects of LDM chemotherapy are empirical or unresolved. These include patient selection, the choice of cytotoxic drug used for treatment, its optimal dose and dosing interval and the nature of other treatment modalities often co-administered.[5,6,9] On average, single doses in LDM regimens tend to be in the range of one tenth to one third of the MTD dose.[1,16] Other questions include the benefits of doublet versus single agent LDM chemotherapy and whether or not treatment efficacy depends on the tumour type. This systematic review aims to evaluate all fully published LDM chemotherapy trials in adults in an attempt to answer the questions raised above.

2. Materials and methods

2.1. Search strategy

The MEDLINE, EMBASE and CENTRAL databases were searched for fully published articles using the key words 'metronomic' and 'chemotherapy' and 'cancer' or 'neoplasm' or 'tumour'. The search was restricted to English language clinical trials from 2000 to April 2012 inclusive. Exclusion criteria included the following: purely translational (companion) studies, paediatric trials, trials with less than 20 patients, studies applying MTD or near-MTD chemotherapy doses, editorials and review articles. An additional PubMed search using the term 'metronomic chemotherapy', limited to English language publications from any time up to and including April 2012, was performed to retrieve any additional articles. A manual search was performed to retrieve relevant studies referenced in the publications identified from the original search. For studies with multiple presentations and/or publications, only the latest versions were included in the analysis.

2.2. Data abstraction and statistical analyses

Two reviewers independently extracted information on study designs, tumour types investigated, patient demographics, regimens applied, efficacy criteria used and reported safety data. Discrepancies were adjudicated by a third reviewer. The absolute dose-intensity (DI, $mg/m^2/week$)[17] of each LDM regimen was calculated and used to obtain the relative dose-intensity (RDI) as compared to the DI of the same agent used in an MTD manner. The MTD DI for a given drug was calculated using data from the Cancer Care Ontario Drug Formulary, unless otherwise indicated (Supplementary Table 1). We assumed that the average body surface area of an adult patient was 1.8 m^2 based on data from the literature.[18,19] We also calculated the dosing-density (DD), defined as the % of days with LDM chemotherapy administration per cycle of treatment. In the event that more than one chemotherapy drug was used metronomically, the DIs were totalled to give a single value for the specified treatment regimen; the same calculation applied for DDs. The DD was then categorised as either greater or equal to 100% (signifying continuous daily treatment with at least one chemotherapy drug) or less than 100%.

Meta-regression analysis using mixed-effect logistic regression (SAS version 9.3, Cary, NC, United States of America (USA)) to account for clustering of patients and outcomes within studies was performed to examine factors associated with disease control rate (DCR), defined as complete response (CR) + partial response (PR) + stable disease (SD). Factors that were considered included RDI, DD, regimen type (singlet LDM,