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Optimal Delivery of Dose in Cancer Chemotherapy with the Support of Haematopoietic Growth Factors

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The delivery of cancer chemotherapy is often non-optimal because of dose reductions and delays related to various toxic effects. These result in a decrease of the dose intensity as well as of the relative dose intensity of a given regimen compared to a reference protocol. In retrospective studies, such modifications have been shown to negatively influence the therapeutic results in many clinical situations. The ability of haematopoietic growth factors to reduce chemotherapy-related neutropenia and its associated infectious complications allows better dose-on-time delivery of the chemotherapeutic drugs. The potential therapeutic impact of this effect remains to be determined in prospective studies.
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INTRODUCTION

CANCER CHEMOTHERAPY is usually delivered in current practice according to a predefined regimen including recommendations for both dosages and timings of drug administration. Doses and schedules are based on the toxicity data from previous phase I and II trials. The toxic effects of each drug as well as the cumulative toxic effects of the combinations of different drugs represent the main limiting factors to an ideally 'optimal chemotherapy'.

Dose reductions and delays are commonly performed in cancer chemotherapy, and initially planned dosages and timings are often significantly modified. The term 'optimal delivery' can be defined as the rare clinical situation where administration of chemotherapy would strictly follow the guidelines of the reference protocol in terms of drugs, doses, schedules and number of cycles.

THE PARAMETERS OF DOSE DELIVERY

Dose intensity

Since the two main parameters of chemotherapy delivery are dose and timing, the dose of chemotherapy delivered per time unit has been proposed to define 'dose intensity' (DI). According to Hryniuk who described the calculation method, "the total number of mg/m^2 is determined for each drug given throughout the 'course of treatment' (defined as the specified number of cycles determined) for each patient. The denominator is then determined by counting the total number of days between the date of first treatment and one cycle after the date of the last treatment. The total number of days of treatment for that patient is then divided by seven to give the number of weeks, and this is used as the divisor to determine the patient's received DI for each drug. In multiagents regimens, the figures are converted to average received DI" [1]. The average received DI for each drug is the arithmetic average of the final received DI for all the patients regardless how many cycles of therapy they received as individuals. The relative DI is the ratio between the received DI and the DI recommended in the chosen reference regimen.

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Dose reductions and delays

Although the majority of cancer patients are treated according to predefined chemotherapy protocols, the use of dose reductions and delays is a very widely spread habit in current oncological practice as well as in prospective controlled clinical trials. Dose reductions can be performed according to predefined guidelines in a given protocol: dose modifications related to the toxicity of the previous cycle(s), fixed doses given to people of all body area surfaces or complete deletion of a drug from the combination. They may also be performed in such uncontrolled ways as rounding of the body surface area or the prescribed dose (for instance, when it is slightly greater than the dose of a single vial or capsule). Dose delays are currently performed to avoid chemotherapy administration during the patient's or the doctor's vacation and to accommodate social schedules. Table 1 gives an example of significant DI reduction in a patient supposed to receive six courses of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as adjuvant chemotherapy for breast cancer. Minimal dose reductions of each of the drugs result in respective relative DIs of 0.94, 0.94 and 0.78 for cyclophosphamide, methotrexate and fluorouracil. For a given patient, these dose modifications result in an average relative DI of 0.89 and compared with 1.0 for the planned treatment. A delay of 4 weeks would result in an additional decrease of the average relative DI to 0.77.

Impact of relative DI on the therapeutic effects

The method proposed by Hryniuk has been widely used to compare the average relative received DI of different multiagent combinations to an arbitrarily chosen reference regimen in order to determine the possible impact of DI on the therapeutic effects of chemotherapy in different tumours. In retrospective studies, the relative received DI has been demonstrated to be significantly correlated with response in metastatic breast cancer [2], relapse-free survival in adjuvant treatment following operable breast cancer [3], and overall survival in ovarian carcinoma [4], Hodgkin's [5] and non-Hodgkin [6] lymphomas and in small cell lung cancer [7]. These data from retrospective analyses must be cautiously interpretated and need to be confirmed in prospective randomised trials. Furthermore, some authors have brought many criticisms to the Hryniuk method which (1) assumes that

Table 1. Example of calculations of dose intensity (see text)

*Predefined protocol (CMF/4 weeks), BS 1.6 M^2					
(C)	100 mg/m^2/day	(160 mg/d)	D 1–14	TDI 350	
(M)	40 mg/m^2/day	(64 mg/d)	D 1 and 8	TDI 20	
(F)	600 mg/m^2/day	(960 mg/d)	D 1 and 8	TDI 300	
*Received protocol ('modified' CMF/4 weeks)					
(C)	150 mg/day		D 1–14	ADI 328	(RDI 0.94)
(M)	60 mg/day		D 1 and 8	ADI 18.75	(RDI 0.94)
(F)	750 mg/day		D 1 and 8	ADI 234	(RDI 0.78)
ARDI = 0.94 + 0.94 + 0.78/3 = 0.89					

*'modified' CMF with a 4 weeks delay. ARDI = 0.89 × (24/28) = 0.77. C = cyclophosphamide; M = methotrexate; F = fluorouracil; TDI = theoretical dose intensity; ADI = administered dose intensity; RDI = relative dose intensity of a given drug; ARDI = average relative dose intensity of the protocol.

all the drugs in a given regimen have the same efficacy, (2) does not take into account the delay before the first course, (3) does not allow the calculation of a cumulative received dose/time, and (4) does not provide individual data for a given patient. Coppin has suggested a more sophisticated calculation method using cumulative plots [8].

THE POTENTIAL IMPACT OF RECOMBINANT HAEMATOPOIETIC GROWTH FACTORS ON DOSE DELIVERY OPTIMISATION

Now that recombinant haematopoietic growth factors (HGF) are clinically available, some of the rules in the management of chemotherapy might change. In fact, the addition of granulocyte colony stimulating factor (G-CSF) or granulocyte–macrophage colony stimulating factor (GM-CSF) to both conventional and high doses of haematotoxic chemotherapy is associated with a significant reduction of the depth and duration of the neutropenic period [9, 10]. Furthermore, this biological effect is associated with a significant reduction of the infectious risk and clinical consequences of neutropenia. In a randomised European trial comparing marrow-ablative chemotherapy followed by either G-CSF or placebo in small cell lung carcinoma, we have demonstrated the capacity of G-CSF to reduce the incidence of febrile neutropenia by half (from 53 to 26% after the first cycle as well as throughout the entire treatment programme). Consequently, the number of days of parenteral antibiotic treatment and the number of days of hospitalisation were also significantly lower [11].

Many clinical trials are ongoing in order to determine the clinical benefit of HGF on 'dose-on-time delivery' of chemotherapy in cancer patients.

Clinical data

Since most of these trials were only recently activated, the results are still preliminary.

Gabrilove *et al.* [12] had previously shown the capacity of G-CSF to allow administration of chemotherapy as scheduled on day 14 using the M-VAC chemotherapy in bladder cancer. The study was not randomised but each patient received chemotherapy with G-CSF in alternating cycles. The neutrophil counts allow day 14 chemotherapy delivery on time in all 18 patients during cycles with G-CSF but only in 5/17 patients not receiving G-CSF.

The most consistent data come from the abovementioned randomised trial in small cell lung cancer [11] in which the delivery of chemotherapy appeared much closer to the reference protocol in the G-CSF arm, than in the placebo arm. The predefined treatment consisted of six courses of a combination of doxorubicin 50 mg/m^2, cyclophosphamide 1 g/m^2 and etoposide 360 mg/m^2. The proportion of patients who experienced at least one cycle with a delay of 2 days or more in the administration of chemotherapy fell from 47% in the placebo arm to 29% in the G-CSF arm. Over all cycles, 69% patients in the placebo arm versus 29% in the G-CSF arm underwent at least one dose reduction of greater than 15%. Finally, the average relative DI was 96% in the G-CSF arm and only 87% in the placebo arm. These figures bring a demonstration of the ability of G-CSF to allow improvement in the delivery of chemotherapy according to the reference protocol in small cell lung cancer. This slight increase in DI did not influence response or survival in this series of patients with small cell lung cancer. Pettengell *et al.* [13] have recently demonstrated similar results in non-Hodgkin lymphoma in a randomised study comparing VAPEC-B with (41 patients) or without (39 patients) G-CSF. Dose reductions were observed in 10% of patients in the G-CSF arm versus 51% in the non-G-CSF arm. The relative DI was greater than 95% in 59% patients receiving G-CSF versus 25% in the control arm.

Further studies are ongoing in order to determine whether or not the adjunction of HGF will allow the DIs to reach high enough levels to influence the therapeutic effects of chemotherapy.

Perspectives

The haematopoietic adverse effects of chemotherapy appear to be the main cause of dose reductions and delays in cancer treatment and might, therefore, be a limiting factor of the therapeutic benefit. Recombinant HGF might offer the possibility of optimising the dose-on-time delivery of chemotherapy. The main point remaining to be solved is knowing whether or not such an improvement in the delivery of chemotherapy in a given protocol might be sufficient to convert an increase of the relative DI into a potential improvement of the therapeutic results. In other words, the only way to test the validity of the retrospective studies performed by Hryniuk is to prospectively analyse the dose and timing data of chemotherapy regimen administered with or without the recombinant HGF support.

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