Gemcitabine: from solid tumor to hematology

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Gemcitabine (2',2'-difluorodeoxycytidine, dFdC) is an analog of deoxycytidine. It is transformed to the active triphosphate(dFdCTP) after intracellular phosphorylation. Gemcitabine monophosphate is inserted into the DNA and inhibits DNA elongation as a false nucleotide. In contrast to other antimetabolites, an additional, altered nucleotide is inserted behind dFdC inhibiting repair mechanisms (masked chain termination).

By this, repair enzymes (exonucleases) of the DNA are inhibited and repair mechanisms are prevented. This factor, as well as enzymic inhibition of gemcitabine diphosphate, lead to high intracellular concentrations of gemcitabine and enforce the cytostatic effect. Gemcitabine is mostly inserted into DNA but partly also into RNA. Competition at the receptor with the nucleoside deoxycytidine phosphate (dCTP) leads to a competitive inhibition of DNA polymerases.[1]

The effects of gemcitabine on cellular metabolism therefore include:
- inhibition of ribonucleotide reductase with lowering/disruption of deoxynucleotide de nove synthesis (mostly dCTP);
- multiplication of effect of deoxycitidine kinase by inhibition of the negative feedback on this enzyme, leading to enhanced phosphorylation of gemcitabine;
- inhibition of the enzyme responsible for the elimination of gemcitabine (deoxycitidine monophosphate deaminase). By exhausting the dCTP pool and increasing the intracellular concentration of dFdCTP, the positive feedback mechanism of the enzyme is further inhibited;
- inhibition of cytidine triphosphate synthetase (CTP-synthetase) leading to a further exhaustion of the dCTP pool and inhibition of RNA synthesis.

Pharmacokinetics

After infusion of 1,000 mg/m^2 of gemcitabine over 30 min, maximal concentrations of 10 to 40 μg/mL are observed. The extracellular half-life is approximately 30 minutes. Gemcitabine is metabolized to the cytostatically inactive metabolite 2'desoxy-2',2'-difluorouridine (dFdU) at a rate of 91-98%. Metabolization occurs in liver, kidneys, blood and other tissues via cytidine deaminases. After infusion of 1,000 mg/m^2, 92-98% of the dose is recovered in urine within one week. The excretion of the original substance and dFdU via the urinary tract is 99% with less than 1% being eliminated in the feces. Cytostatically active metabolites of gemcitabine are not detectable in plasma or urine. The plasma protein binding of gemcitabine is only 10%.

So far, gemcitabine has been found to demonstrate a broad spectrum of activity in solid tumors, including pancreatic, ovarian, breast, lung and bladder cancers. In hematopoietic malignancies, gemcitabine has shown a high level of activity as a single agent in relapsed or refractory Hodgkin's disease (HD) and some degree of efficacy in aggressive and indolent non-Hodgkin's lymphoma (NHL).

Hodgkin's disease

The study reported by Santoro[2] *et al.*, was the first to evaluate the activity of gemcitabine in patients with previously treated HD. The drug dose was 1,250 mg/m^2 intravenous infusion on days 1,8, and 15 of each 28-day cycle of therapy. The incidences of complete and partial responses were promising and strongly suggested a possible role for this drug in the management of HD. Of the 22 patients, two patients (9%) reached a state of complete remission, and seven patients (30%) achieved a partial response, for an overall response rate of 39%. The likelihood of achieving a response was not influenced by the patients' main pretreatment characteristics or by their response to their last prior chemotherapy. The median duration of response was 7 months, and the median overall survival time was 11 months. In addition, in our experience[3] 3 of 14 pretreated patients we obtained an overall response rate of 43% with 2 (14%) patients who achieved complete remission

and 4 (29%) patients who had a partial response. In particular, both patients who had relapsed after autologous bone marrow transplantation achieved a response. The gemcitabine dose was 1,200 mg/m^2 with the same schedule as that used by Santoro. Another positive experience was reported by Lucas *et al.*[4]

Recently, the German Hodgkin Lymphoma Study Group started a study developing a BEACOPP variant (BAGCOPP) with the intention to reduce the rate of acute and long-term toxicities (particularly secondary malignancies) while maintaining or improving the regimen's efficacy by replacing etoposide with gemcitabine. The primary objective of the phase I part of the study is the determination of the maximum tolerated dose (MTD) of gemcitabine with regard to the timely and adequately dosed application of the therapeutic regimen. Three patients will be included at each dose level consecutively (800, 1000, 1250, 1500, 1750 mg/m^2 etc, at days 1 and 4, respectively). After reaching dose limiting toxicities and the determination of the MTD of gemcitabine, the phase II part of the BAGCOPP study will start. About the rationale for the treatment schedule, current information concerning gemcitabine comes from studies in solid tumors and lymphomas in which single doses of 750 to 2,500 mg/m^2 have been investigated with infusions lasting between 30 and 70 minutes. The maximum dose used was 4,560 mg/m^2. Almost all protocols included three single doses one week apart from each other followed by a one-week rest period. Only a few studies tested multiple infusions within one week or at longer intervals. The hematologic substances cyclophosphamide, adriamycin and etoposide will be given at the start of each cycle (days 1 to 3) in the BEACOPP protocol in order to allow adequate stem cell recovery. Two single administrations of gemcitabine on days 1 and 4 are planned in the BAGCOPP protocol with the aim of adhering to this principle. In the light of pharmacokinetic data, three days of rest between two gemcitabine administrations are regarded feasible.

Aggressive non-Hodgkin's lymphoma

A multicenter phase II trial was conducted by Fossa *et al.*,[5] in patients with relapsed or refractory aggressive NHL. Thirty patients with B-cell intermediate or high-grade NHL were enrolled into the study. No complete responses were observed, but six patients showed a partial response, 11 stable disease, and 13 progressive disease. The overall response rate was 20%. The median duration of partial response was 6 months. All patients who responded had a histologic diagnosis of diffuse large cell lymphoma whereas no patient with a diagnosis of intermediate- or high-grade lymphoma other than diffuse large-cell lymphoma showed a response. No statistically significant association with response rates was found for any clinical parameter. Notably, three patients with a complete response and three patients with no response after the last combination chemotherapy responded to gemcitabine. This study demonstrated the moderate efficacy of gemcitabine in the setting of relapsed or refractory aggressive lymphoma. It is difficult to compare these response rates to results reported in phase II trials using other drugs as single agents in patients with relapsed or refractory NHL. Furthermore, independent confirmatory studies evaluating the same drug are frequently missing. Considering these difficulties, the observed efficacy and toxicity of gemcitabine compare well with results of studies using single agents that are frequently incorporated in combination chemotherapy regimens for treatment of aggressive NHL, such as etoposide, mitoxantrone, or cisplatinum. The results also seem interesting when compared with those tram other novel chemotherapeutic agents under investigation in NHL, such as paclitaxel or the topoisomerase I inhibitors CPT-II.

Other experiences have been described in aggressive NHL. Particularly, Savage et al.,[6] reported that gemcitabine showed substantial activity in heavily pretreated middle-aged to elderly patients with advanced aggressive NHL. In this study the maximum dose of gemcitabine was 1000 mg/m^2 given weekly and the drug was infused, as in previous studies, aver 30 minutes. Based on pharmacokinetic data, it is possible that a prolonged infusion might be more effective and less toxic.[7,8] On this basis, in a new ongoing phase II study Savage et al have increased the infusion time from 30 to 180 minutes.

Bernell and Ohm also reported responses in two out of three patients with aggressive lymphoma treated with a dose of 800 mg/m^2/week.[9]

Indolent NHL

The study reported by Dumontet *et al.*,[10] represented the first trial evaluating the efficacy of gemcitabine as a single agent in patients with relapsed or refractory indolent lymphomas. Thirtyfive patients were enrolled into the study, including 11 cases of mantle celi lymphoma (MCL), 10 cases of chronic lymphocytic leukemia (CLL)/lymphocytic lymphoma, nine cases of follicular lymphoma, four cases of lymphoplasmacytic lymphoma and two cases of T-celllymphoma. Gemcitabine 1000 mg/m^2 was administered as a 30-min infusion on days 1,8 and 15 of a 28-day schedule, up to a maximum of six cycles. Complete responses were observed in two patients with MCL, and partial responses were observed in seven patients, including three patients with CLL/lymphocytic lymphoma, two patients with T-cell lymphoma, one patient with MCL and one patient with follicular lymphoma. The overall

response rate for the entire patient population was 25%. In addition, minor responses were observed in three patients, including two patients with MCL, and one patient with CLL. The median duration of response was 150 days and the overall progression-free survival was 342 days. There was a trend towards longer progression-free survival in patients who had not received prior nucleoside analog therapy than in patients who had received such therapy. Preclinical data had shown significant *in vitro* efficacy on B-CLL cells and myeloma cell lines.[11,12]

T-cell disorders

Concerning cutaneous T-cell lymphoma (CTCL) , we conducted a phase II trial in 44 consecutive, previously treated patients with mycosis fungoides (MF) (30 cases) and peripheral T-cell lymphoma unspecified (PTCLU) (14 cases) with exclusive skin involvement. Gemcitabine was given to all patients on days 1,8, and 15 of a 28-day schedule at a dose of 1,200 mg/m^2 for a total of three cycles. Of the 44 patients, five (11.5%) achieved complete responses, 26 (59%) partial responses, and the remaining 13 showed no benefit from the treatment. Two of the complete responses were histologically confirmed. The complete and partial response rates were the same far patients with MF and those with PTCLU, respectively. No difference in terms of overall response rate was observed between relapsed and refractory patients. The median durations of complete response and partial response were 15 months and 10 months, respectively. This report has confirmed our preliminary data on 13 patients,[14] who are also included here with a longer follow-up; in this study, gemcitabinetreated patients had a higher or at least comparable overall response rate compared with literature data on patients with MF treated with other nucleoside analogs, such as fludarabine and pentostatin.

Recently, we started a phase IIb multicenter study with gemcitabine as primary chemotherapy of patients with advanced CTCL (or pretreated only with PUVA or radiotherapy). The patients will be recruited from the Italian Cutaneous Lymphoma Study Group.

Sallah et al.,[15] reported their experience in 10 patients with refractory and relapsed T-cell malignancies treated with gemcitabine. Two patients had CTCL, 2 prolymphocytic leukemia (PLL), 2 nodal PTCL, 2 small lymphocytic lymphoma (SLL), 1 anaplastic and 1 angiocentric lymphoma. The drug dose was the conventional 1,200 mg/m^2 on days 1, 8 and 15 of each 28-day cycle. Of the 10 patients, two achieved a complete response (1 PLL and 1 anaplastic) and four a partial response (2 CTCL, 1 angiocentric, 1 PTCL) for an overall response rate of 60%. The median and mean duration of response was 13 and 16 months, respectively.

Toxicity

Hematologic toxicities: anemia ofWHO grade III was observed in 5-10% of patients, neutropenia of WHO grades III and IV in 20% and 10% of patients, respectively, WHO grade III and IV thrombocytopenia in 20% and 10% of patients, respectively.

Non-hematologic toxicity: transient elevations in liver transaminases were observed in 5-10% of patients. Renal and pulmonary toxicity was very rare; WHO grade III-IV less than 1%. Flu-like symptoms with headache, fever, myalgias and fatigue occurred in up to 10% of patients. No alopecia usually occurs during gemcitabine therapy. Neurotoxicity in connection with gemcitabine is rare. Peripheral edema occurs in 10% of patients. These toxicities were usually mild and reversible after the end of therapy.

Conclusions

Its modest toxicity profile and the easy schedule of administration make gemcitabine an ideal agent for consideration in the development of chemotherapy regimens. In particular, it would be interesting to evaluate the use of two different nucleoside analogs (fludarabine or pentostatin plus gemcitabine) in modulating the entry route into DNA and their action in terms of direct cytoxicity and apoptosis, respectively. Earlier investigations demonstrated the possibility of potentiating fludarabine with low doses of gemcitabine[16] In addition, administration of antibody Campath-1 H, which has demonstrated activity in T-PLL, in combination with gemcitabine may provide a unique mechanism of cell killing and prove to be an effective regimen in T-cell malignancies. Given the efficacy of regimens combining cytarabine and cisplatin in lymphoid malignancies, and the experience of combinations of gemcitabine with platinum compounds in solid tumors, combinations of gemcitabine with other compounds should be investigated. Preliminary interesting data have been reported by Emmanouilides et al.,[17] on a gemcitabine, cisplatin and dexamethasone combination in patients with multiply relapsed Hodgkin's and non-Hodgkin's lymphoma.

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