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Activity of combined gemcitabine therapy on treatment of planocellular carcinoma: A pilot study

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ABSTRACT

BACKGROUND: *Drug-orientated, pilot study was conducted to estimate the activity of gemcitabine on treatment of head and neck and lung planocellular carcinoma in combination with either radiotherapy or chemotherapy.*

METHODS: *There were 22 patients treated with gemcitabine for planocellular carcinoma of head and neck (9 patients) and lung (13 patients). Combined gemcitabine-radiotherapy was applied in 10 patients while gemcitabine-chemotherapy in 12 patients. Eligible and evaluable patients (22) were with either locally advanced (14 patients) or metastatic (8 patients) stage of the disease. In gemcitabine-radiotherapy group, gemcitabine was given IV, 1000 mg/ m^2, on day 1, 8, and 15 during the radiotherapy course as radiopotentiator (65 Gy in 32 fractions for head and neck, and 55 Gy in 20 fractions, split course one month for lung cancer patients). In gemcitabine-chemotherapy group the same dose of gemcitabine was given (4-week schedule) in combination with platinum based cytotoxic drugs. We analyzed response rate and toxicity.*

RESULTS: *Among patients treated for head and neck planocellular carcinoma, there were 67% complete responders while there was 15% complete responders treated for lung cancer. Also, 80% of patients treated in gemcitabine-radiotherapy group had complete response while 50% of those treated in gemcitabine-chemotherapy group. Actuarial survival as function of tumor control was 52% for lung and 88% for head and neck cancer, 12 months after the initiation of treatment. In gemcitabine-radiotherapy group of patients treated for head and neck carcinoma, the radiation mucositis grade III was observed in 80% while in gemcitabine - chemotherapy group of patients the most common side effect (60% of patients) was neutropenia grade II (40%)/III (20%).*

CONCLUSION: *There was no statistically significant difference regarding response rate between two groups of patients (head and neck vs. lung cancer, and gemcitabine- radiotherapy vs. gemcitabine - chemotherapy). However, better clinical results were achieved for head and neck cancer patients, particularly in gemcitabine - radiotherapy group but with significant toxicity due to high gemcitabine dose.*

KEY WORDS: *Deoxycytidine; Head and Neck Neoplasms; Lung Neoplasms; Carcinoma, Squamous Cell; Antineoplastic Combined Protocols*

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INTRODUCTION

Gemcitabine (2'2'-Difluorodeoxycytidine) is a deoxycytidine analog with clinical activity against several solid tumors, such as ovarian cancer, non-small cell lung cancer, head and neck carcinoma, and pancreatic cancer. After entering the cell, gemcitabine is phosphorylated to its triphosphate (dFdCTP) which can be incorporated into DNA, followed by one more deoxynucleotide after which DNA-polymerization stops, which probably determines its cytotoxic effect. Besides this effect, dFdCTP is also capable of inhibiting ribonucleotide reductase, an enzyme with a key role in DNA repair mechanisms (1-2). The cytotoxic activity of gemcitabine strongly correlates with the amount of dFdCTP incorporated into cellular DNA. *In vitro* studies suggest that gemcitabine activity is schedule dependent. Weekly intravenous administration in heavily pretreated patients has been associated with maximum tolerated doses (MTD) ranging from 790 to 1370 mg /m^2/ week. This schedule has been selected for optimizing activity and minimizing clinical toxicity. Hematological toxicity of gemcitabine given as weekly injection consists of moderate reversible neutropenia and thrombocytopenia. Liver dysfunction is characterized by an increase of the level of transaminase enzymes but it is usually mild and noncumulative, and infrequently requires treatment discontinuation. Other toxicities have been reported consisting of flu-like syndrome in less than 20% of patients, edema occurring in 30% of patients, and cutaneous allergic rash. Several phase II trials have investigated the safety and the efficacy of gemcitabine in combination with classical cytotoxic drugs in patients with non-small cell lung cancer, small cell lung cancer, breast, bladder, head and neck, ovarian, and pancreatic cancer (3-8). Patients with advanced stage squamous cell carcinoma of the head and neck generally have a poor prognosis with a median duration of survival between 4 and 6 months. Even with the use of chemotherapy in multimodality regimens, survival times for patients with metastatic and/or recurrent disease have not changed dramatically during the past few decades (9). Gemcitabine is a radiosensitizing agent. Preclinical data suggest that

depletion of dNTP pools (specifically dATP) correlates with observed radiosensitization. Phase I studies combining radiotherapy and low-dose gemcitabine have shown interesting activity in head and neck and pancreatic cancer, in part with severe side effects. In order to evaluate the toxicity and efficacy of a combination of radiotherapy and low-dose gemcitabine in locally advanced or recurrent head and neck and thyroid tumors, a phase II study was performed with gemcitabine 200 mg/m^2 IV weekly during radiotherapy. Scalliet et al., report on a trial conducted from October 1994 through August 1995; gemcitabine 1000 mg/m^2 was administered weekly (six weeks) along with thoracic radiotherapy, 2 Gy daily fraction, 5 days/week, during six weeks (60 Gy). Eight patients were enrolled but the study was terminated due to excessive toxicity. There were three treatment related deaths. Gemcitabine is a potent radiation sensitizer and its role will be further defined in ongoing controlled clinical trials (10 -12).

Gemcitabine is a novel nucleoside analogue with activity in a range of preclinical models both *in vitro* and *in vivo*. It is highly schedule dependent, 3 times weekly every 4 weeks being the recommended schedule for phase II/III studies. Early phase II trials identified activity against non-small cell lung cancer and pancreatic cancers, tumor types for which gemcitabine has a license for treatment in many countries. However, preclinical models have indicated that gemcitabine may be active against many other human solid tumors. In phase II studies activity has been identified against breast cancer, both as a single agent and in combination. In bladder cancer, impressive single agent activity of gemcitabine has also been seen, as well as in combination with cisplatin, initially in MVAC (methotrexate + vinblastine + doxorubicin + cisplatin) and platinum failures, but more recently as first line therapy both as a single agent and combined with cisplatin. Antitumor activity has also been seen in patients with ovarian cancer, head and neck cancer, small cell lung cancer and cervical cancer, with minimal activity in renal carcinoma, prostate and colon cancer. In view of the excellent side effect profile and the potential for gemcitabine to inhibit DNA repair after exposure to DNA damaging agents, further developments of gemcitabine will include its use in combination chemotherapy and combined modality schedules (13 -14).

Aim of our study: Drug orientated, pilot study was conducted to estimate the activity of gemcitabine on treatment of head and neck and lung planocellular carcinoma, in combination either with radiotherapy or chemotherapy.

PATIENTS AND METHODS

Patients with histologically confirmed planocellular carcinoma of the head and neck and lung carcinoma were enrolled into nonrandomized, drug orientated-pilot study, phase II, at the Oncology Clinic, Clinical Center of Montenegro, Podgorica, from January 2001 to January 2002. There were 22 patients treated with gemcitabine for head and neck carcinoma (9 patients) and lung carcinoma (13 patients). Combined gemcitabine-radiotherapy was applied in 10 patients while gemcitabine-chemotherapy in 12 patients (Table 1).

Eligible and evaluable patients (22) were with either locally advanced (14 patients) or metastatic (8 patients) stage of the disease (Table 2).

Table 1. Patients' groups

Number of patients	Head and neck group (9)	Lung group (13)
Gemcitabine-radiotherapy group (10)	5	5
Gemcitabine-chemotherapy group (12)	4	8

Table 2. Stage of the disease

Number of patients	Head and neck group (9)	Lung group (13)	Gemcitabine – radiotherapy group (10)	Gemcitabine – chemotherapy group (12)
Locally advanced disease (14)	5	9	8	6
Metastatic disease (8)	4	4	2	6

Eligibility criteria also included Eastern Cooperative Oncology Group performance status of 0 to 2, measurable disease, adequate hematologic function (granulocyte count >1.500/μL, hemoglobin level >10 g/dl and platelet count >100 000/μL), adequate renal function (serum creatinine concentration <2.0/dl), and a life expectancy greater than 3 months. A complete history and physical examination of all patients was performed before treatment. In gemcitabine radiotherapy group gemcitabine was given IV, 1000 mg/m^2 on day 1, 8, and 15 as a 30-minute infusion during the radiotherapy course as radiopotentiator. For head and neck an initial 45 Gy in 2 Gy daily fractions, 4.5 weeks was delivered to the tumor and regional lymph nodes. The boosted volume included the original tumor volume with 1 cm margin and an additional 20 Gy in 2 Gy daily fractions, 2 weeks. The spinal cord dose was limited to 45 Gy. Two lateral opposite beam arrangements and 6 MeV photon energies were required, linear accelerator, Clinac 600 C, Varian.

For lung cancer an initial 30 Gy in 3 Gy daily fractions, 2 weeks was delivered to the tumor and mediastinal lymph nodes with 1 cm margin and after 1 month split course 25 Gy in 2.5 Gy daily fractions, 2 weeks only to the tumor with 0.5 cm margin. Three or four beam arrangements according to Report 50 of the ICRU (International Commission on Radiation Units and Measurements) and the same energy were required (linear accelerator, Clinac 600 C, Varian). In gemcitabine-chemotherapy group same dose of gemcitabine was given (4 weeks schedule) in combination with cisplatin at a dose of 100 mg / m^2 on day 2. We analyzed response rate and toxicity. Response was evaluated following standard World Health Organization (WHO) criteria. Complete response required the disappearance of all measurable or assessable disease signs and symptoms. Toxicity was assessed according WHO criteria. The values were compared by chi square test. Patients' survival was calculated with life table method.

RESULTS

The median age was 53.5 years (range: 39-74 years). Of the 22 patients entered into the study, 8 patients had metastatic disease and 14 patients locally advanced disease at the time of enrolment. All patients with localized disease had unresectable tumor. Among patients treated for head and neck planocellular carcinoma, there were 67% complete responders while there was 15% complete responders treated for lung cancer. Also, 80% of patients treated in gemcitabine-radiotherapy group had complete response while 50% of those treated in gemcitabine-chemotherapy group. In gemcitabine-radiotherapy group of patients treated for head and neck carcinoma the radiation mucositis grade III was observed in 80% while gemcitabine-chemotherapy group of patients the most common side effect (60% of patients was neutropenia grade II [40%] and grade III [20%]) (Table 3).

Actuarial survival as function of tumor control was 52% for lung and 88% for head and neck cancer, 12 months after the initiation of treatment.

DISCUSSION

In summary, it appears that gemcitabine has the activity in planocellular carcinoma. The combination of gemcitabine plus cisplatin should be considered one of the more effective combinations especially in advanced non-small cell lung cancer. This combination should be evaluated in earlier stage disease (i.e. adjuvant surgical trials) to see if the modest impact on survival in patients with metastatic disease may translate into improvement in long-term survival in patients with potentially curable disease (10). Alternating chemoradiotherapy was shown to be superior to standard radiation in patients with unresectable squamous cell carcinoma of the head and neck. Gemcitabine has shown in vitro and in vivo radiosensitizing properties, synergistic activity with cisplatin, and cytotoxic activity against unresectable squamous cell carcinoma of the head and neck. Considering the expected

Table 3. Patients' characteristics

All patients = 22	
Gender:	
Male = 17 patients	
Female = 5 patients	
Age:	
30 – 39 = 1 patient	
40 – 49 = 7 patients	
50 – 59 = 5 patients	min = 39, max = 74, median = 53.5 years
60 – 69 = 7 patients	
70 – 79 = 2 patients	
Performance status:	
2 = 2 patients	
1 = 14 patients	
0 = 6 patients	
Localization of the disease:	
Head and neck carcinoma = 9 patients	
Lung carcinoma = 13 patients	
Stage of the disease:	
Locally advanced = 14 patients	
Metastatic = 8 patients	
Therapy:	
Gemcitabine – Radiotherapy group = 10 patients	
Gemcitabine – Chemotherapy group = 12 patients	
Toxicity:	
Nonhematological toxicity = mucositis G III (80%) - (gemcitabine-radiotherapy group)	
Hematological toxicity = neutropenia G II (40%) / G III (20%) – (gemcitabine - chemotherapy group)	

poor prognosis of the enrolled patients, this combined regimen showed an impressive anti-tumoral activity, but the severity of correlated associated hematological toxicity makes the application of this regimen unproposable. However, the activity observed warrants the exploration of different, less toxic, chemo-radiotherapy programs including gemcitabine (15). Only phase III trials will be able to confirm this promise of activity and tolerability Gemcitabine is a potent radiation sensitizer and its role will be further defined in ongoing controlled clinical trials.

CONCLUSION

In our study there was no statistically significant difference regarding response rate between two groups of patients (head and neck vs. lung cancer and gemcitabine-radiotherapy vs. gemcitabine-chemotherapy) ($p > 0.05$). However, better clinical results were achieved for head and neck cancer patients, particularly in gemcitabine-radiotherapy group with significant toxicity due to high gemcitabine dose. However, in our study there were not treatment toxicity related deaths.

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