Abstract #912P

SALVAGE THERAPY IN RECURRENT OVARIAN CANCER: A COMBINATION OF GEMCITABINE AND TREOSULFAN IS EQUALLY ACTIVE IN PLATINUM-RESISTANT AND PLATINUM-SENSITIVE DISEASE

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ABSTRACT

Aim: The prognosis of heavily pretreated patients (pts) with epithelial ovarian carcinoma (EOC) and related malignancies having failed multiple chemotherapy (CTx) regimens is poor, irrespectively of the individual platinum-resistance status. In preceding studies, the combination of treosulfan and prolonged low-dose gemcitabine (GeT) has shown promising activity in platinum-resistant EOC. This non-interventional study has been set up in order to obtain more detailed informations regarding the clinical value of GeT given under routine conditions.

Methods: 59 pts with recurrent EOC (n=54), fallopian tube cancer (FTC; n=2), peritoneal papillary-serous carcinoma (PPSC; n=2), and type II endometrial carcinoma (EC-II; n=1) who did not qualify for recruitment into a controlled clinical trial were included in this study. Pts had failed a median of 3 (range 1-11) prior Ctx, 37 were platinum-resistant (group R) and 22 were sensitive (group S). GeT was administered for 1-11 q2w cycles with treosulfan at 1 g/m² PO on days 1-4 and gemcitabine at 450 mg/m² IV (3 hour infusion) on day 1. Adverse effects were scored according to CTCAE 4.0, responses were classified according to the integrated GCIG criteria. PFS and OS were calculated from the start of GeT until progression or death from any reason or loss to follow up.

Results: GeT was generally well tolerated. Hematological side-effects were frequent but manageable with G3-4 neutropenia seen in 6, G3-4 anemia in 8, G3 fever in 3, and G4 infection in 1 pt. Non-hematological toxicities exceeded G2 in only 4 pts. In 1 pt, GeT was prematurely stopped due to toxicity (allergic exanthema). A total of 8 CR and 19 PR accounted for an ORR of 45.8%. Adding 16 pts with SD, the clinical benefit rate (CBR) was 72.9%. PFS was 17.3 weeks (wks) and OS was 67.6 wks. No significant differences between groups R and S were found in regard to ORR (40.5 vs 54.5%), CBR (70.3% vs 77.3%), PFS (17.0 vs 18.4 wks), and OS (63.0 vs 72.6 wks). Moreover, prior Ctx with one of the single agents did not lower the likelihood to benefit from GeT.

Conclusions: GeT given under routine conditions is well-tolerated and efficacious in heavily pretreated pts with recurrent EOC, FTC, PPSC, and EC-II by exhibiting chemodulatory properities. Its particularly promising activity in platinum-reistant disease should be further explored in large-scaled prospective clinical trials.

BACKGROUND

The prognosis of patients (pts) suffering from platinum-resistant epithelial ovarian cancer (EOC) and related malignancies is poor as is that of those presenting with principally platinum-sensitive disease who have failed multiple preceding chemotherapies (CTx). The combination of treosulfan (TREO), a ^{7}N-alkylator, and gemcitabine (dFdC) has been primarily developed for the treatment of malignancies with a high degree of intrinsic chemoresistance such as metastatic uveal melanoma [1]. Subesequently, this combination has been successfully used to treat other refractory tumors including platinum-resistant EOC [2-5]. However, it has been found that a traditional q3w schedule combining TREO at 5 g/m² given on day 1 and dFdC at 1,000-1,250 mg/m² (30 min infusion) on days 1 and 8 resulted in a high incidence of hematological side effects, which although not deteriorating the likelihood of response had a negative impact of response-duration [2]. Therefore, we have developed a q2w schedule (GeT) combining low-dose prolonged gemcitabine (450 mg/m²) on day 1 with oral TREO at daily doses of 1,000 mg/m² given over four consecutive days. In a phase II study in patients with platinum- and taxane-resistant EOC, GeT has shown an impressive activity with an objective response rate (ORR) of 51%, a progression-free survival (PFS) of 27 weeks (wks) and an overall survival (OS) of 76.5 wks [4]. Despite these promising results, GeT has been only occasionally used in the clinical routine. This non-interventional study in heavily pretreated pts with EOC and related malignancies has been undertaken in order to yield detailed insights into the value of GeT administered under clinical routine conditions.

PATIENTS AND METHODS

A total of 59 pts with recurrent EOC (n=54), fallopian tube cancer (FTC, n=2), peritoneal papillary-serous carcinoma (PPSC, n=2), and type-II endometrial cancer (EC-II, n=1) who did not qualify to be recruited into a controlled clinical trial were included in this study. In regard to the *Markman* criteria, 37 pts were platinum-resistant (group R) whereas 22 pts were platinum-sensitive (group S). Pts had failed a median of 3 preceding CTx regimens (range: 1-11), including platinum and taxanes in all of them. Additionally, 18 pts (30.5%) have been previously exposed to other dFdC or TREO containing regimens. 10 of these pts were platinum-resistant. Detailed patients´ characteristics are summarized in Table 1. Pts had received 1-11 cycles of GeT at a 2qw schedule with oral TREO at 1,000 mg/m²/d given on day 1-4 and dFdC at 450 mg/m² given as a 3 hour infusion on day 1 of each cycle. Standard anti-emetic treatment consisted of granisetrone at 3 mg or tropisetrone at 5 mg and dexamethasone at 8 mg given on days 1 through 4. Primary G-CSF prophylaxis was not prescribed; secondary G-CSF could be given if indicated. Adverse effects were scored according to CTCAE 4.0. Responses were classified to the integrated GCIG criteria [6]. PFS was calculated from the start of GeT therapy and subsequent onset of disease progression, OS was calculated from the start of GeT and death from any reason, progression or loss to follow-up, whatever occurred first.

Table 1: Patients´characteristics

	No. of patients
Age	
Median	59 yrs
Range	32-78 yrs
Tumor type	
Epithelial ovarian carcinoma	54
Fallopian tube carcinoma	2
Peritoneal papillary-serous carcinoma	2
Type II endometrial carcinoma	1
Clinical platinum-resistance	
Platinum-resistant	37
Platinum-sensitive	22
No. of prior systemic treatments	
Median	3
Range	1-11
1-2 prior Ctx	29
3-11 prior Ctx	30
Prior Ctx with dFdC or TREO	18

Table 2: Adverse effects related to GeT

	Any grade	Grade 3-4
Hematological		
Neutropenia	13	6
Anemia	27	8
Thrombocytopenia	6	0
Thrombocytosis	1	0
Fever	11	3
Infection	8	1
Non-hematological		
Nausea	18	2
Constipation	4	0
Diarrhea	3	0
Pain	4	0
Arthralgia/myalgia	3	0
Skin rash	6	0
Fluid retention	2	0
Fatigue	3	1

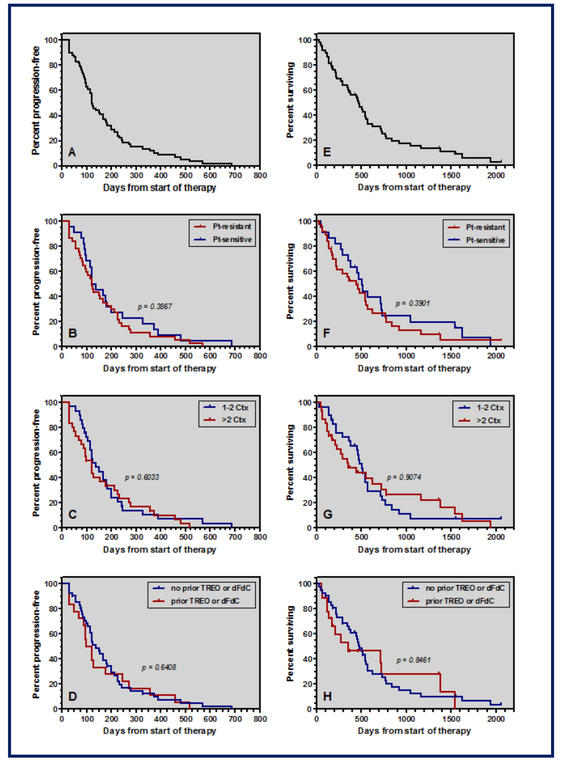

Figure 1: Long-term survival following GeT. A-D, progression-free survival; E-H, overall survival. A,E whole study population; B, F, comparison between platinum-resistant and platinum-sensitive pts; C, G, comparison between less and more intensively pretreated pts; D, H, comparison between gemcitabine /treosulfan pretretreated pts and gemcitabine/treosulfan naïve pts.

Table 3: Antineoplastic efficacy of GeT

	Total	Group R	Group S	1-2 prior Ctx	> 2 prior Ctx	Prior dFdC/TREO	No prior dFdC/TREO
CR	8	5	3	2	6	5	3
PR	19	10	9	13	6	2	17
SD	16	11	5	10	6	4	12
PD	16	11	5	4	12	7	9
ORR	45.8%	40.5%	54.5%	51.7%	40.0%	38.9%	48.8%
CBR	72.9%	70.3%	77.3%	86.2%	60.0%	61.1%	78.0%
PFS	17.3 wks	17.0 wks	18.4 wks	17.0 wks	19.6 wks	15.6 wks	19.6 wks
OS	67.6 wks	63.0 wks	72.6 wks	51.0 wks	72.6 wks	51.0 wks	69.0 wks

RESULTS

Toxicities seen with GeT are summarized in Table 2. Generally, GeT was well tolerated. As expected from previous trials, hematological side effects were frequent but mostly manageable: 6 pts had G3-4 neutropenia, 8 pts experienced G3-4 anemia. G3 fever was seen in 3 pts and G4 infection in 1 pt. Non-hematological toxicities rarely exceeded G2. In 1 pt, GeT was prematurely finished due to allergic exanthema. Response data are shown in Table 3. ORR was 45.8% with 8 CR, 19 PR, 16 SD, and 16 PD. The clinical benefit rate (CBR) was 72.9%. Median PFS was 17.3 wks and median OS was 67.6 wks. The corresponding features for groups R and S were: ORR, 40.5% vs 54.5%; CBR, 70.3% vs 77.3%; PFS, 17.0 vs 18.4 wks; OS, 63.0 vs 72.6 wks. None of the observed differences reached statistical significance. Moreover, more intensively pretreated patients (i. e. > 2 preceding CTx) had almost the same likelihood of response and survival as those with less intensive pretreatment (< 2 preceding CTx): ORR, 40.0% vs 51.7%; CBR, 60.0% vs 86.2%; PFS 17.0 wks vs 19.6 wks; OS, 51.0 wks vs 72.6 wks. Only the difference in CBR reached statistical significance (p=0.0391). Comparing pts pretreated with either dFdC or TREO with those not having such a prior therapy, again, no major differences were observed in regard to both response and survival: ORR, 38.9% vs 48.8%; CBR, 61.1% vs 78.0%, PFS; 15.6 wks vs 19.6 wks; OS, 51.0 wks vs 69.0 wks. Survival curves are shown in Figure 1.

CONCLUSIONS

- GeT in recurrent EOC and related malignancies given under routine clinical conditions is feasible and safe
- GeT mainly produces hematological side-effects which like non-hematological toxicities are generally manageable
- In the entire group of pts, GeT showed a promising activity with an ORR similar to that seen in previous studies with less intensively pretreated pts and both a PFS and OS which are clinically meaningful
- GeT is active even after multiple treatments and can thus be used for later-line therapy of EOC and related cancers
- Pretreatment with either TREO or dFdC did not adversely influence the likelyhood to respond to GeT
- **GeT is one of the very few regimens that is equally active in pts with platinum-sensitive and –resistant disease**
- The last two findings support the opinion, that dFdC is rather a chemomodulator than a cytostatic by itself potentiating the activity of both platinum analogues and alkylating agents like TREO
- GeT should be seriously considered for salvage therapy of intensively pretreated EOC and related malignancies even in platinum-resistant pts who have already been exposed to combinations with dFdC and platinum compounds

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