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Tumour Review

Palliative treatment of germ cell cancer

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ABSTRACT

Most patients with metastatic germ-cell cancer (GCC) can be cured by cisplatin-based combination chemotherapy. Yet, about 10–15% of metastatic GCC patients will eventually die of their disease. This narrative review focuses on treatment options when cure is no longer realistic.

Introduction

Germ-cell cancers (GCC) are a unique example of a curable malignant disease [1]. Therefore, palliative treatment is rarely being discussed. Yet, 10–15% of metastatic patients will fail first as well as subsequent lines of platinum-based treatments and eventually die of their disease [2]. Palliative treatment of patients with GCC remains challenging with little high-level evidence to support decision making in this situation.

Who is "palliative" among GCC patients?

There is good evidence that subsets of patients with multiple relapses, and, to a lesser extent, patients with primary cisplatin-refractory disease may still be cured by conventional-dose (CDCT), high-dose chemotherapy (HDCT) and/or desperation surgery delivered as first, second or subsequent salvage treatment [2–8]. Therefore, patients will usually have had multiple lines of chemotherapy including HDCT before being considered palliative. The same applies to patients unfit for HDCT failing three or more lines of CDCT [2,9]. The majority of patients will have received modern type cisplatin- and ifosfamide-based salvage regimens such as cisplatin, ifosfamide and vinblastine (VeIP), etoposide (VIP) or paclitaxel (TIP) [2,9]. Desperation surgery might still salvage individual patients of these two cohorts [5–7]. However, if desperation surgery cannot successfully be performed, patients failing HDCT or three or more lines of CDCT face little or no realistic hope for cure. Therefore, a palliative treatment population can be defined as patients failing salvage HDCT or patients unfit for HDCT who fail three or more lines of CDCT in whom desperation surgery cannot be successfully be performed. Rare exceptions to this definition may occur. With respect to the many early clinical trials investigating different systemic treatment approaches for refractory GCC patients, life-extension remains the primary goal for the majority of patients. As reported in the following sections, responses are generally short-lived, which is why alleviation of pain and other symptoms to enhance the patients' quality-of-life is also desired. However, quality-of-life was not routinely assessed as a trial end point in the majority of available studies and has to be considered individually as a main goal, whichever treatment is being chosen. To provide a better understanding of the efficacy and toxicities associated with palliative treatments, common adverse events for the different treatment options are mentioned in the tables.

Single agent chemotherapy

Single agent activity has been reported for paclitaxel [10–14], gemcitabine [15,16], oxaliplatin [17,18], oral etoposide [19], ifosfamide [20], and oral temozolomide [21] mainly in small phase I/II trials in patients with cisplatin-refractory disease. Responses were mainly partial remissions or disease stabilizations. However, sequential single agent treatment is an appropriate option in addition to best-supportive-

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Table 1
Single agent regimens.

Drug	Schedule			N Patients	Previous HDCT	ORR	Duration of benefit for responders (measure, median, range) [months]	Relevant toxicities ≥grade 3	Ref
Gemcitabine	1000 mg/m^2 iv.	d1,8,15	q3w	31	71%	19%	TTF, 4+ (2–9+)	Granulocytopenia 13% Thrombocytopenia 22%	15
	1200 mg/m^2 iv.	d1,8,15	q3w	20	55%	15%	PFS, n.r. (2–6)	Neutropenia 10% Thrombocytopenia 30% Nausea 5%	16
Oxaliplatin	60 mg/m^2 iv. 130 mg/m^2 iv.	d1,8,15 d1	q3w q2w	16 16	78%	6% 19%	PFS, n.r. (2–8)	Granulocytopenia 9% Thrombocytopenia 16% Nausea/vomiting 6% Neurotoxicity 3%	17
	130 mg/m^2 iv.	d1	q3w	8	NR	25%	PFS, n.r.	n.r.	18
Paclitaxel	135–310 mg/m^2 iv.	d1	q3w	10	NR	20%	DOR, n.r. (3–5)	Granulocytopenia 90% Infection 10%	14
	170 mg/m^2 iv.	d1	q3w	18	16%	11%	PFS, n.r. (1.5–2)	Granulocytopenia 67% Anemia 7% Neutropenic fever 17% Neurotoxicity 13%	13
	225 mg/m^2 iv.	d1	q3w	24	50%	25%	DOR, 8+ (3–16+)	Granulocytopenia 50% Thrombocytopenia 16% Severe infections 12% Neurotoxicity ≥°II 27% Mucositis °II/III 16%	11
	250 mg/m^2 iv.	d1	q3w	15	13%	13%	DOR, n.r. (9–10 weeks)	Neutropenia 87% Thrombocytopenia 73% Peripheral neuropathy °II/III 53%	12
	250 mg/m^2 iv.	d1	q3w	31	16%	26%	n.r.	Mainly hematologic Neurotoxicity °III 19% Mucositis °II/III 16% Liver function test > 5xULN 10%	10
Ifosfamide	2000 mg/m^2 iv.	d1-5	q3w	30	NR	23%	DOR, 3.5 (2–5.5)	Neutropenia 52% Thrombocytopenia 20% Nausea/vomiting 43%	20
Oral Etoposide	50 mg/m^2 po.	d1-14	q3w	21	29%	14%	n.r.	Granulocytopenia 36% Febrile granulocytopenia 23%	19
Oral Temozolomide	150–200 mg/m^2 po.	d1-5	q4w	20	40%	10%	DOR, 1.5 (3.5–9)	Thrombocytopenia 10% Anemia 5%	21

DOR, duration of response; PFS, progression-free survival; TTF, time to treatment failure; n.r., not reported.

care in the palliative setting of patients with a poor performance status asking for further active treatment in order to avoid the more frequent side-effects of combination chemotherapy. Table 1 provides an overview of single-agent chemotherapy regimens.

Combination chemotherapy

Combinations of drugs with single-agent activity result in higher response rates compared to using single-agent treatment alone. The triple combination of gemcitabine, oxaliplatin and paclitaxel (GOP) reported the highest response rates so far with more than 50% objective responses and even few long-term remissions (Table 2) [22–25]. Doublet combinations of these drugs may also provide favorable responses ranging from 4% to 46% (Table 3) [26–31]. Other doublets include cisplatin, plus epirubicin [32] or irinotecan [33], or oxaliplatin together with the VEGF-targeted antibody bevacizumab [34] or again irinotecan [35]. Other triple combination regimens comprise of paclitaxel, cisplatin and gemcitabine (TPG) (ORR 49%) [36], or oxaliplatin, irinotecan and paclitaxel (IPO) followed by one cycle of topotecan-based HDCT (ORR 49%) [37]. Recently, clinical activity and good tolerability of the combination of etoposide, methotrexate and actinomycin D, alternating with cyclophosphamide and vincristine (EMA/CO), as established for female gestational trophoblastic disease, has been reported in patients with refractory GCC and elevated levels of human chorionic gonadotrophin [38] (Table 2).

Taken together, combination chemotherapy seems to be the most promising palliative approach in medically fit patients with a good performance status in whom the toxicities of a doublet or a triple combination seem acceptable. Direct comparisons of combination treatments have not been published, and none of the regimens have proven unequivocal superiority.

Targeted treatments and immunotherapy

Investigational agents include tyrosine kinase inhibitors, i.e. sunitinib [39,40], sorafenib [41], imatinib [42], tivantinib [43] and pazopanib [44] as well as anti-angiogenic agents, i.e. thalidomide [45] and lenalidomide [46], and the mTOR inhibitor everolimus [47] amongst many others (Table 4). However, apart from single case reports, all these agents failed to induce clinically meaningful responses in unselected patient cohorts [48]. Similarly, antibody-drug conjugate brentuximab-vedotin was investigated in CD30-positive, refractory GCC patients. Some responses were observed but tended to be short-lived [49,50]. Thus, the results of investigational agents are conflicting, and at present these drugs have no established role in the palliative treatment setting of GCC.

Immunomodulatory treatment with immune checkpoint inhibitors active against the programmed- cell death receptor (PD-1) or ítś ligand (PD-L1) are currently being investigated also in refractory GCC as many tumors were shown to express PD-L1 [51]. However, application of the PD-1-directed monoclonal antibody pembrolizumab failed to induce clinically meaningful responses in a phase II trial enrolling 12 patients, which was terminated prematurely [52]. In another phase II trial, the anti-PD-L1 antibody Durvalumab alone yielded no responses among 9 GCC patients, whereas the combination with the CTLA-4 antibody tremelimumab achieved clinical responses in 2 out of 9 heavily pretreated GCC patients [53]. Other immune checkpoint inhibitors are currently under investigation, i.e. single agent treatment with the PD-L1 antibody

Table 2
Triple-drug regimens.

Drug	Schedule			Patients	Previous HDCT	ORR	Duration of benefit for responders (measure, median, range) [months]	Relevant toxicities ≥ grade 3	Ref
Gemcitabine	800 mg/m[b] iv.	d1&8	q3w	41	78%	51%	PFS, 3 (1–17 +)	Granulocytopenia 15%	24
Oxaliplatin	130 mg/m[b] iv.	d1	q3w					Anemia 7%	
Paclitaxel	80 mg/m[b] iv.	d1&8	q3w					Thrombocytopenia 49%	
								Neurotoxicity 2%	
								Nausea/Emesis 2%	
								Diarrhea 2%	
Gemcitabine	800 mg/m[b] iv.	d1&8	q2w	30	20%	31%	PFS, 6.5 (95%CI, 3.2–27.5)	Neutropenia 17%	25
Oxaliplatin	100–125 mg/m[b] iv.	d1	q2w					Febrile Neutropenia 7%	
Paclitaxel	170 mg/m[b] iv.	d1	q2w					Gastrointestinal °II/III 12%	
								Neuropathy 5%	
Cisplatin	50 mg/m[b] iv.	d1&8	q3w	75	13%	DCR 67%	PFS, 5 (95%CI, 4–8)	Anemia 28%	36
								Neutropenia 29%	
Gemcitabine	800 mg/m[b] iv.	d1&8	q3w					Febrile Neutropenia 5%	
Paclitaxel	80 mg/m[b] iv.	d1&8	q3w					Thrombocytopenia 40%	
								Ototoxicity 4%	
Oxaliplatin	100 mg/m[b] iv.	d1	q3w	43	0% (74% subsequent HDCT)	49%	2-year PFS 21%, (median n.r.)	Neutropenia 33%	37
Irinotecan	200 mg/m[b] iv.	d1	q3w					Thrombocytopenia 16%	
Paclitaxel	80 mg/m[b] iv.	d1,8,15	q3w					Neuropathy 2%	
								Nause/Emesis 4%	
								Diarrhea 12%	
Etoposide	100 mg/m[b] iv.	d1&2	q2w	41	39%	29%	PFS, 3 (95%CI, 2–4)	Hematologic 39%	38
Methotrexate[a]	300 mg/m[b] iv.	d1	q2w						
Folinic acid[b]	15 mg × 4 iv./po.	d2&3	q2w						
Actinomycin D	0.5 mg/m[b] iv.	d1&2	q2w						
Vincristine	1 mg/m[b] iv.	d8	q2w						
Cyclophosphamide	600 mg/m[b] iv.	d8	q2w						

DCR, disease control rate (complete + partial remissions + stable disease); DOR, duration of response; PFS, progression-free survival; TTF, time to treatment failure, HDCT, high-dose chemotherapy.

[a] Methotexate given as continuous infusion over 12 h.

[b] Folinic acid started 24 h after methotraxate for 4 doses every 12 h.

Atezolizumab (NCT02458638), or the PD-1 antibody Nivolumab (NCT02832167) in phase II basket trials. Moreover, combined treatment approaches, such as the anti-PD-1 antibody Nivolumab plus anti-CTLA-4 antibody Ipilimumab, are also currently being evaluated (NCT02834013).

Choosing the right treatment for the right patient

Finding the right treatment for the right patient at the right time is obviously key to any palliative strategy in GCC patients. A formal comparison of available palliative regimens was not attempted in this review, as cohorts of published series are notoriously small and pretreatments too heterogeneous to allow a meaningful approach. However, the large number of small studies indicates the lack of unequivocal superiority of any given regimen. Many palliative patients will receive sequential lines of treatments often switching from a combination to a single-agent regimen until available options are exhausted. An algorithm to support treatment selection is given in Fig. 1.

Challenging scenarios in palliative GCC patients

Brain metastases

Palliative patients with GCC and brain metastases should still receive radiotherapy for symptom control, delivered either as stereotactic or total brain irradiation depending on the number and location of the metastases as well as the local availability of the respective techniques. Patients who are “fit” for chemotherapy may be treated with multimodality strategies of chemotherapy and irradiation. In the palliative setting neurosurgery is rarely indicated [54].

Bone metastases

Patients suffering metastatic bone disease may undergo multimodal treatment including chemotherapy and radiotherapy to alleviate skeletal symptoms, if a limited number of symptomatic bone metastases are present. The use of anti-resorptive agents, e.g. bisphosphonates or RANKL-inhibitors can be considered, although data on their use in GCC patients is lacking [55].

Peripheral neuropathy

The majority of palliative GCC patients experience peripheral neuropathy as a result of exposure to cisplatin, to taxanes or to HDCT. Treatment options and high-level evidence are limited, but the use of co-analgesic medication, e.g. the antidepressants duloxetine, amitryptiline or venlafaxine and/or the anticonvulsants gabapentin or pregabalin may alleviate symptoms [56]. Often peripheral neuropathy will limit or prohibit the further use of cisplatin, oxalipatin or the taxanes.

Early integration of palliative care and psychosocial support

Similar to patients suffering from other malignancies, palliative patients with GCC may benefit from early integration of a specialized palliative care team in order to professionally identify and treat many of the additional symptoms and needs common to palliative cancer patients [57]. Particularly, the young age of patients with GCC increases their vulnerability for psychological distress. Studies have emphasized a strong correlation between young age and higher levels of anxiety and depression among patients and their relatives [57]. Therefore, psychological support must be an integral part of any palliative strategy in GCC patients.

Table 3
Doublet regimens.

Drug	Schedule			Patients	Previous HDCT	ORR	Duration of benefit for responders (measure, median, range) [months]	Relevant toxicities ≥ grade 3	Ref
Gemcitabine Oxaliplatin	1000 mg/m^2 iv. 130 mg/m^2 iv.	d1&8 d1	q3w q3w	35	89%	46%	DFS, n.r. (2–16+)	Leukocytopenia 54% Thrombocytopenia 48% Anemia 11% Febrile Neutropenia 9% Treatment-related death 3% Neurotoxicity 9% Nausea/Emesis 16% Diarrhea 6%	26
Gemcitabine Oxaliplatin	1000 mg/m^2 iv. 130 mg/m^2 iv.	d1&8 d1	q3w q3w	28	14%	32%	DFS, n.r. (2–28+)	Neutropenia 62% Febrile Neutropenia 10% Thrombocytopenia 41% Anemia 21% Neurotoxicity 10% Nausea/Emesis 27% Fatigue 17%	27
Gemcitabine Oxaliplatin	1250 mg/m^2 iv. 130 mg/m^2 iv.	d1&8 d1	q3w q3w	18	22%	17%	DFS, n.r. (18+ - 44+)	Neutropenia 39% Thrombocytopenia 22% Anemia 11% Peripheral Neuropathy 17% Asthenia 11% Nausea/Vomiting 5%	28
Paclitaxel Oxaliplatin	175 mg/m2 iv. 130 mg/m2 iv.	d1 d1	q3w q3w	26	19%	4%	TTP, 1.4 (95%CI 0–14.8)	Neutropenia 30% Thrombocytopenia 4% Anemia 12% Neuropathy 1% Nausea/Emesis 8% Fatigue 4%	29
Bevacizumab Oxaliplatin	10 mg/kg iv. 85 mg/m^2 iv.	d1&8 d1	q3w q2w	24	54%	29%	DOR, 6 (4–22)	Peripheral neuropathy Hypertension Seizuress Deep vein thrombosi	34
Oxaliplatin Irinotecan	85 mg/m^2 iv. 80 mg/m^2 iv.	d1&15 d1,8,15	q4w q4w	18	0	39%	DFS, n.r. (2–19+)	Neutropenia 17% Thrombocytopenia 17% Anemia 12% Neurotoxicity 11% Nausea/Emesis 28% Diarrhea 22% Mucositis 11%	36
Cisplatin Epirubicin	20 mg/m^2 iv. 90 mg/m^2 iv.	d1-5 d1	q3w q3w	30	13%	57%	NED, n.r. (n.r. – 48+)	Neutropenia 13% Febrile Neutropenia 3% Thormbocytopenia 7% Anemia 17% Neuropathy 7% Nausea/Vomiting 27% Diarrhea 3% Nephrotoxicity 7%	32
Cisplatin Irinotecan	20 mg/m^2 iv. 100–150 mg/m^2 iv.	d1-5 d1&15	q4w q4w	11	27%	45%	DOR, n.r. (12+–140+)	Neutropenia 18% Thrombocytopenia 17% Anemia 14% Nausea/Vomiting 8% Diarrhea 5%	33
Paclitaxel Gemcitabine	110 mg/m^2 iv. 1000 mg/m^2 iv.	d1,8,15 d1,8,15	q4w q4w	28	36%	21%	DOR, n.r. (2–25+)	Neutropenia 54% Febrile Neutropenia 4% Thrombocytopenia 32% Anemia 11% Neuropathy 4% Nausea/Emesis 8% Fatigue 8%	30
Paclitaxel Gemcitabine	100 mg/m^2 iv. 1000 mg/m^2 iv.	d1,8,15 d1,8,15	q4w q4w	32	100%	31%	NED, n.r. (22+–54+)	n.r.	31

DFS, disease-free survival; DOR, duration of response; NED, no evidence of disease; PFS, progression-free survival; TTF, time to treatment failure; n.r., not reported.

Conclusion

Guidance of treatment and care of refractory GCC patients in the palliative setting is challenging and emotionally demanding. Although some cytotoxic agents have shown efficacy either as single agents or as part of drug combinations, survival is limited and durable remissions are rare. The most difficult decision is when to stop cancer-directed treatments altogether and switch to best-supportive care alone. On the technical side, we suggest as one cornerstone of care close contact with an expert GCC center that cares for such patients regularly. Locally, early integration of specialized palliative care as outlined by the American Society of Oncology [58] is the second cornerstone that supports symptom control and alleviates suffering for all parties involved.

Table 4
Targeted treatment approaches and immunotherapy.

Drug	Molecular target	Patients (n)	ORR (%)	Med. PFS (months)	Ref
Sunitinib	VEGFR, KIT, PDGFR, RET	33	13	2.0	39
		10	0	n.r.	40
Sorafenib	VEGFR, KIT, PDGFR, RAF	18	0	n.r.	41
Pazopanib	VEGFR, PDGFR	9	0	n.r.	44
Imatinib mesylate	KIT	6	0	n.r.	42
Tivantinib	MET	21	0	1.0	43
Everolimus	mTOR	15	0	1.7	47
Thalidomide	Anti-angiogenic	15	0	3.0	45
Lenalidomide	Anti-angiogenic	4	0	n.r.	46
Brentuximab- vedotin	CD30	5	40	n.r.	49
		9	22	n.r.	50
Pembrolizumab	PD-1	12	0	n.r.	52
Durvalumab	PD-L1	9	0	n.r.	53
Durvalumab + Tremelimumab	PD-L1	9	22	n.r.	

CTLA-4, cytotoxic T-lymphocate-associated protein 4; KIT, stem cell growth factor receptor; MET, hepatocyte growth factor receptor; ORR, objecitve repsonse rate (complete and/or partial remissions); PD-1, programmed death 1; PD-L1, programmed death ligand 1; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RAF, rapidly accelerated fibrosarcome oncogene family; RET, reaaranged during transfection proto-oncogene; VEGFR, vascular endothelial growth factor receptor; n.r., not reported.

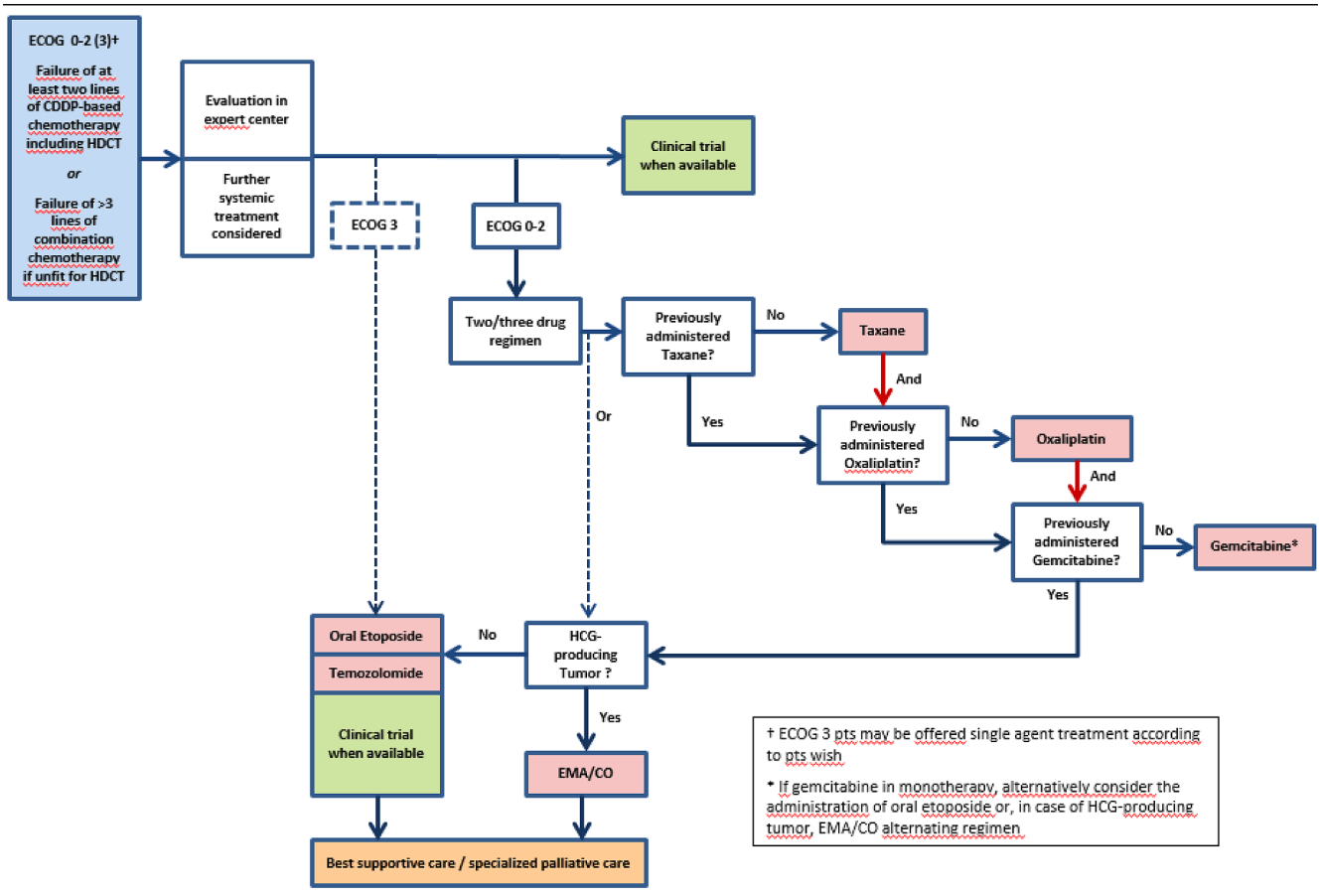

Fig. 1. Treatment algorithm for selection of palliative treatments.

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