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TOPIC PAPER

Platinum-refractory germ cell tumors: an update on current treatment options and developments

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Abstract
Purpose In general, 50 % up to 80 % of metastasized germ cell tumor patients can be cured by platinum-based chemotherapy. However, 3–5 % of patients will still die of platinum-refractory disease and new systemic treatment options are needed to improve treatment success in this difficult setting. This review aims to give an overview on treatment options and current developments in the field of platinum-refractory male germ cell tumors.
Methods A comprehensive literature search was conducted searching PubMed, Medline, Cochrane and Embase to identify clinical trials regarding the treatment of platinum-refractory disease. ASCO, EAU and ESMO conference proceedings were searched to identify unpublished results of relevant trials. Comprehensive review papers were hand searched for additional references. Clinicaltrials.gov was checked for ongoing clinical trials in the field of platinum-refractory germ cell tumors.
Results Outcome of platinum-refractory disease remains poor. Single-agents with reasonable activity are gemcitabine, oxaliplatin and paclitaxel, but complete remissions resulting in long-term survival could not be achieved. The triple-combination of gemcitabine, oxaliplatin and paclitaxel followed by resection of residual masses provides the best outcomes with objective responses in 51 % of patients and long-term survival in approximately 10–15 %. To date, no molecularly targeted agent has shown reasonable activity.
Conclusions Treatment options for platinum-refractory disease are limited, but a small subset of patients may achieve long-term disease-free survival by multimodal treatment. The potential of novel targeted agents, i.e. by immune-checkpoint-inhibition remains to be defined.

Keywords Germ cell tumor · Germ cell cancer · Platinum-refractory · Salvage chemotherapy · Targeted therapy · Salvage surgery

Introduction

Germ cell tumors (GCTs) are the most common malignancies among adolescent and young adult men. The incidence has been rising steadily worldwide over the past 50 years and is highest in Northern and Central Europe [1].

GCTs are a model of curable cancer with cure rates among the highest in solid tumors of more than 90 % of all patients, and of 70–80 % even in disseminated disease [2–4]. However, 10–15 % of patients will fail cisplatin-based first-line treatment and need salvage treatment, including patients with cisplatin-refractory (initial response or stabilization during chemotherapy with subsequent relapse or progression within 4 weeks after the end of treatment) and absolute cisplatin-refractory disease (progression despite ongoing chemotherapy) [5]. First salvage treatment may achieve a sustained complete remission in about 40–50 % of relapsed patients [6]. Subsequent relapses are clinically challenging, as they confer a substantially poor prognosis with a limited life expectancy of only a few months [7]. In general, 3–5 % of GCT patients potentially die of their cancer [8].

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Treatment options after failure of cisplatin-based combinations and high-dose chemotherapy are limited. Several conventional single-agents have shown reasonable activity in vitro and in vivo with objective response rates of 10–37 %, but complete responses were rarely achievable (3–10 %). However, since the patients are usually of younger age, lack comorbidities and have preserved organ functions, combination chemotherapy of active single-agents is utilized more often with improved response rates of 40 % up to 60 % and complete responses in 5–30 % [9]. However, long-term remissions are scarce. The most effective regimen defined so far is the triple-combination of gemcitabine, oxaliplatin and paclitaxel, by which long-term remissions could be achieved in 11 % of patients if combined with subsequent resection of residual masses [10, 11].

Definition of molecular markers for therapeutic targeting has improved the treatment of many malignancies [12]. However, in germ cell tumors, no such predictive biomarkers or molecular targets could be established, yet. Molecularly targeted single-agent therapies with tyrosine kinase inhibitors, such as sunitinib, pazopanib or sorafenib, or with anti-angiogenic agents (lenalidomide, thalidomide), were investigated in several phase I/II trials with disappointing results [13]. The role of immunomodulatory checkpoint-inhibition by targeting CTLA-4 or PD-1 remains to be elucidated.

Methods

A comprehensive literature search was conducted searching PubMed, Medline and Embase to identify articles reporting on clinical trials regarding the treatment of platinum-refractory disease from 1980 until present. ASCO, ESMO, AUA and EAU conference proceedings from 2010 until present were searched to identify unpublished results of relevant trials. Comprehensive review papers were hand searched for additional references. Clinicaltrials.gov was searched for ongoing clinical trials in the field of platinum-refractory germ cell tumors. Case reports and small patient series were excluded from the current review.

Results

Single-agent chemotherapy

Based on promising preclinical activities, several conventional chemotherapeutic drugs have been investigated in phase I/II trials in platinum-refractory patients. Clinical activity of paclitaxel, gemcitabine, oxaliplatin or continuously applied oral etoposide, ifosfamide and temozolomide was overall limited with objective responses achieved in 10–37 %, but complete responses and long-term remissions were rarely observed [14, 15]. Other agents, i.e. bendamustine, topotecan, ixabepilone or epirubicin, did not show relevant anti-tumor activity. Data on single-agent and doublet combination salvage chemotherapy regimens are summarized in Table 1.

Combination chemotherapy

Despite intensive pretreatment, platinum-refractory patients are often eligible for further combination chemotherapy approaches due to their usually younger age, the lack of comorbidities and preserved organ functions. Therefore, combinations of the aforementioned single-agents and other even cisplatin-based combinations have been investigated in phase II trials in the last decade. Overall, objective response rates were better with approximately 20–40 % as compared to single-agent treatment, and median overall survival (OS) of 6–8 months was achieved, but still long-term remissions remained scarce (5–10 %) (Table 1).

The most effective regimen so far was a triple-combination of gemcitabine, oxaliplatin and paclitaxel (GOP) investigated by the German Testicular Cancer Study Group (GTCSG). In a phase II trial, GOP achieved a remarkable ORR of 51 % in 41 refractory or multiply relapsed patients, of which 78 % had relapsed after high-dose chemotherapy. Two patients achieved a CR by systemic treatment alone, another five patients, who were considered unresectable prior to chemotherapy, had no evidence of disease (NED) after surgical resection of residual masses [11]. After a median follow-up of 19 months, seven patients (17 %) were >2 years free of disease (one patient relapsed after GOP but achieved NED status after further salvage treatment). Median OS was 17 months for patients achieving a CR or partial remission (PR). Given the high proportion of secondary CRs following resection of residual masses (five of seven patients), aggressive secondary surgery seems to be important for successful salvage treatment [10]. The activity of the GOP regimen was confirmed in another phase II trial with a bi-weekly schedule. In this trial, the ORR was 31 %, with a CR in 2 of 30 patients (7 %). Moreover, another 17 % of the patients, who were initially considered unresectable, became NED after secondary surgery [16]. In a retrospective analysis of 75 patients, the triple-combination of gemcitabine, cisplatin and paclitaxel achieved comparably favorable results in refractory GCTs with an ORR of 49 % (11 % CR), and 44 % of patients underwent secondary resection. Of note, patients achieving NED had a significantly prolonged OS of 71 months compared to 12.5 months in those who did not [17].

Consequently, multimodal treatment consisting of preferably triple-combination systemic treatment (GOP)

Table 1 Conventional salvage chemotherapy regimens for refractory GCT patients

Regimen	Dose	Author	Year	Pts (*n*)	Prior HD-CT (%)	ORR (%)	CR (%)
Single-agent regimens							
Gemcitabine	1000 mg/m^2 IV d1, 8, 15, q3w	Bokemeyer	1999	31	71	19	0
	1200 mg/m^2 IV d1, 8, 15, q4w	Einhorn	1999	20	55	15	5
Oxaliplatin	60 mg/m^2 IV d1, 8, 15 q4w						
	85 mg/m^2 IV d1 + 15 q4w	Kollmannsberger	2002	16	78	13	0
				16		37	0
	130 mg/m^2 IV d1, q3w	Fizazi	2004	8	NR	25	0
Paclitaxel	250 mg/m^2 IV d1, q3w	Motzer	1994	31	16	26	10
	135–310 mg/m^2 IV d1, q3w	Bokemeyer	1994	10	NR	20	0
	225 mg/m^2 IV d1, q3w	Bokemeyer	1996	24	50	25	8
	250 mg/m^2 IV d1, q3w	Nazario	1995	15	13	7	0
	170 mg/m^2 IV d1, q3w	Sandler	1998	18	16	11	0
Oral etoposide	50 mg/m^2/day continuously	Millller	1990	21	29	14	0
Ifosfamide	2000 mg/m^2 IV d1-5, q3w	Wheeler	1986	30	NR	23	3
Temozolomide	150–200 mg/m^2 PO d1-5, q4w	Maroto	2011	20	40	10	0
Doublet combination regimens							
Gemcitabine	1000 mg/m^2 IV d1, 8, q3w	Kollmannsberger	2004	35	89	46	9
Oxaliplatin	130 mg/m^2 IV d1, q3w						
Gemcitabine	1000 mg/m^2 IV d1, 8, q3w	Pectasides	2004	28	14	32	14
Oxaliplatin	130 mg/m^2 IV d1, q3w						
Gemcitabine	1250 mg/m^2 IV d1, 8, q3w	De Giorgi	2006	18	22	17	6
Oxaliplatin	130 mg/m^2 IV d1, q3w						
Paclitaxel	175 mg/m^2 IV d1, q3w	Theodore	2008	26	19	4	0
Oxaliplatin	130 mg/m^2 IV d1, q3w						
Bevacizumab	85 mg/m^2 IV d1, q2w	Jain	2011	24	54	29	0
Oxaliplatin	10 mg/kg IV d1, q2w						
Oxaliplatin	85 mg/m^2 IV d1, 15, q4w	Pectasides	2004	18	0	39	22
Irinotecan	80 mg/m^2 IV d1, 8,15, q4w						
Cisplatin	20 mg/m^2 IV d1-5, q3w	Bedano	2006	30	13	57	30
Epirubicin	90 mg/m^2 IV d1, q3w						
Cisplatin	20 mg/m^2 IV d1-5, q4w	Miki	2002	11	27	45	9
Irinotecan	100–150 mg/m^2 IV d1, 15, q4w						
Paclitaxel	110 mg/m^2 IV d1, 8, 15, q4w	Hinton	2002	28	36	21	11
Gemcitabine	1000 mg/m^2 IV d1, 8, 15, q4w						
Paclitaxel	100 mg/m^2 IV d1, 8, 15, q4w	Einhorn	2007	32	100	31	19
Gemcitabine	1000 mg/m^2 IV d1, 8, 15, q4w						
Triple-combination regimens							
Gemcitabine	800 mg/m^2 IV d1, 8, q3w	Bokemeyer	2008	41	78	51	5
Oxaliplatin	130 mg/m^2 IV d1, q3w						
Paclitaxel	80 mg/m^2 IV d1, 8, q3w						
Gemcitabine	800 mg/m^2 IV d1, q2w	Sadeghi	2013	30	20	31	7
Oxaliplatin	100–125 mg/m^2 IV d1, q2w						
Paclitaxel biweekly	170 mg/m^2 IV d1, q2w						
Oxaliplatin	200 mg/m^2 IV d1, q3w	Shamash	2007	28	0	71	18
Irinotecan	200 mg/m^2 IV d1, q3w						
Paclitaxel	80 mg/m^2 IV d1, 8, 15, q3w						

CR complete remission, *HD-CT* high-dose chemotherapy, *NR* not reported, *ORR* objective response rate

and subsequent secondary resection is the current recommended treatment for cisplatin-refractory patients or patients relapsing after high-dose chemotherapy (HD-CT).

Combination chemotherapy plus regional deep hyperthermia

Mild hyperthermia at 40.5–43 °C has been shown in vitro and in vivo to enhance the cytotoxicity of some cytotoxic agents and is widely applied as part of limb perfusion or intraperitoneal chemotherapy [18]. The MAKEI study group evaluated the combination of salvage conventional dose chemotherapy with etoposide, ifosfamide and cisplatin (VIP) plus loco-regional hyperthermia in a phase II trial including 44 pediatric and young adolescent patients aged from 7 months to 21 years with loco-regional relapsed and/or refractory (12 patients) germ cell tumors. Of 35 evaluable patients, 30 patients (86 %) achieved an objective response (including 16 complete remissions) and a 5-year event-free survival rate of 62 % by multimodal treatment including radiotherapy of post-chemotherapy residual masses [19]. Despite a heterogeneous patient population, the beneficial impact of hyperthermia seems impressive, and further investigation of this approach is awaited. However, relapsed and refractory disease is rarely loco-regionally limited, which limits the feasibility of this approach.

High-dose chemotherapy for multiply relapsed disease

Salvage HD-CT and subsequent autologous stem cell transplantation is a reasonable treatment option for patients failing first-line systemic treatment. Cure rates of about 50–55 % have been reported by retrospective analyses [5, 20, 21]. However, for patients failing conventional dose salvage treatment, the benefit of dose-intensified treatment is less evident with response rates of 55 %, but only limited long-term survival of 17 % after HD-CT as second-salvage treatment [22]. Therefore, HD-CT as salvage treatment for second or further relapse cannot be generally recommended. In fact, refractory and multiply relapsed patients should be referred to expertise centers to individually identify the optimal treatment option.

Molecularly targeted therapy

Potential biomarkers

The extraordinary sensitivity of GCTs toward cisplatin has been assigned to wild-type p53 leading to an enhanced induction of apoptosis upon cisplatin-treatment. On the other hand, different mechanisms contributing to cisplatin-resistance in GCTs have been unraveled in vitro in the last decades [23].

TP53 mutations or amplification of the p53-inhibiting MDM2 occur in about 25 % of cisplatin-refractory GCTs [24]. MDM2 is a downstream target of AKT and thus part of the PI3K–AKT signaling pathway, which has been suggested to be involved in tumor growth and cisplatin-resistance of GCTs [23, 25]. Mutations of *PI3K* and *AKT1* can be found occasionally [26]. Furthermore, loss of the expression of the PI3K-inhibitor PTEN has been described in about 60 % of cisplatin-resistant GCTs, suggesting overactivation of PI3K–AKT signaling [27]. As a consequence, targeting the PI3K–AKT signaling cascade may hold promise in refractory GCTs. Oncogenic pathways like PI3K–AKT are activated by receptor tyrosine kinases. Refractory GCTs were described to highly express vascular endothelial growth factor receptor 2 (VEGFR-2), platelet-derived growth factor receptor β (PDGFR β) and cKIT in preclinical models [28]. Overexpression of the VEGFR-ligand VEGF may be associated with metastatic disease status [29]. Moreover, oncogenic activation of the mammalian target of rapamycin (mTOR) pathway promotes cell growth, survival and proliferation in various cancers, which deemed mTOR an interesting target for anti-cancer treatment [30].

Other oncogenic drivers like mutations of *Ras* family members (i.e., *KRAS*, *NRAS*, *HRAS*) are found in 7–25 % resistant GCTs, preferably in seminomas [26, 27, 31]. Moreover, the oncogenic *BRAF* V600E mutation leads to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway and has been associated with refractory GCTs, but not with sensitive controls in a histopathological study [32], but a second study failed to confirm these findings [26].

Furthermore, immunotherapy by checkpoint-inhibition is evolving rapidly and has led to fast and enduring responses in several malignancies, even in advanced and refractory patients. Programmed death-1 (PD-1), a surface receptor displayed on regulatory T cells, and its ligand PD-L1 play a critical role in T cell co-inhibition helping cancer cells to elude T cell-mediated cytotoxicity. Overexpression of PD-1 and/or PD-L1 on cancer cells and tumor-infiltrating immune cells was shown to negatively correlate outcome in several malignancies, which is why targeting the PD-1/PD-L1 axis evolved [33]. In a histopathological examination of 486 GCT samples, 52 % have been found to overexpress PD-L1, particularly the more undifferentiated subtype seminoma (69 %) and embryonal carcinoma (61 %) [34]. Therefore, targeted checkpoint-inhibition may be promising in a relevant proportion of GCT patients.

Molecularly targeted treatment

Several targeting agents, as described in the following, have been investigated in refractory GCT patients over the

last decades, but overall activity was limited, and objective responses were rarely achieved. However, in none of the trials patients have been selected based on the presence of potential biomarkers.

Targeting the retinoic acid receptor Targeting the retinoic acid receptor by all-trans retinoic acid (ATRA) may have growth-inhibitory effects in solid tumors, which has also been shown for GCTs in vitro. But, two early phase II clinical trials ATRA failed to induce objective responses in refractory GCTs [35, 36].

Arsenic trioxide In preclinical systems, arsenic trioxide (ATO) had antiproliferative and proapoptotic in solid tumors and ATO-induced apoptosis is sought to be p53-independent. However, in a phase II trial including 20 refractory GCT patients no responses were seen [37].

Targeting the DNA repair machinery Cisplatin induces DNA interstrand crosslinks, which may lead to double-strand break (DSB) formation. Unrepaired DSBs inevitably cause cell death by mitotic catastrophe. Homologous recombination (HR) is a main DSB repair pathway and frequently dysregulated in various malignancies. Embryonal carcinoma cell lines have been shown to be HR-insufficient and to consequently be susceptible to poly(ADP-ribose) polymerase (PARP) inhibition by olaparib. A clinical trial of olaparib in refractory GCT patients is currently ongoing (NCT02533765).

Targeting the retinoblastoma pathway The retinoblastoma pathway involves several cyclin-dependent kinases (CDK), such as CDK4, which is known to activate the retinoblastoma tumor-suppressor protein (Rb) and cyclin D2. GCTs have been found to frequently overexpress CDK4, while Rb is expressed predominantly in mature GCT components (i.e., teratomas) [38, 39]. High expression of Rb promotes cell growth, which is why targeting of CDK4 seems promising. The selective CDK4/6 inhibitor palbociclib was evaluated in a phase I basket trial including three patients suffering growing teratoma syndrome. Two patients achieved disease stabilization for 18 and 24 months, respectively, and one patient had a partial remission lasting 22 months [40]. In a subsequent phase II trial including 30 patients with Rb overexpressing GCT, 28 % achieved 24-week progression-free survival as the primary end point [41]. Particularly, patients with unresectable teratoma and teratoma with malignant transformation benefited from palbociclib with a meaningful delay of disease-related clinical events in their incurable treatment setting [42].

Targeting epigenomic alterations Targeting epigenetic phenomena of cancer cells, i.e., promoter hypermethylation or histone modifications, has shown to be active particularly in hematologic malignancies. In GCTs, particularly non-seminomas, which are more likely to develop cisplatin-resistance, show subtype-specific methylation profiles and demethylating agents like 5-Azacytidine were shown to sensitize GCT cells to cisplatin-treatment in vitro [43]. However, initial clinical trials of both single-agents, 5-Azacytidine and 5-Aza-2′-deoxycytidine, yielded disappointing results [44, 45].

Antiangiogenic treatment Antiangiogenic treatment with thalidomide only induced tumor marker declines in 5 of 15 patients in a phase II trial, but no objective responses were achieved [46]. The less-neurotoxic lenalidomide did not show any activity in refractory GCTs [47].

Another option to target tumor angiogenesis is bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF). Bevacizumab has been investigated as part of combination regimens together with oxaliplatin or as part of a high-dose chemotherapy regimen. Bevacizumab plus oxaliplatin was evaluated in 24 patients, of which 54 % had received prior HD-CT. Of 24 evaluable patients, 7 (29 %) responded objectively and median survival was limited with 8 months and only one patient achieved NED status for >12 months [48]. Tandem HD-CT including bevacizumab was tested in 43 patients and achieved a high objective response rate of 89 %, but the study population was heterogeneous including 14 % cisplatin-sensitive patients, the cytostatic drug regimens were unusual (gemcitabine, docetaxel, melphalan and carboplatin (GemDMC) (first cycle), and ifosfamide, carboplatin and etoposide (second cycle)), and there was excess treatment-related toxicity with four treatment-related deaths [49]. Therefore, bevacizumab-based combination chemotherapy cannot be recommended to date.

Receptor tyrosine kinase inhibition Targeting cKIT by imatinib mesylate only had very limited activity in a phase II trial of six non-seminoma patients, of which one achieved a disease stabilization [50]. VEGFR and PDGFR signaling can be inhibited by tyrosine kinase inhibitors (TKI), such as sunitinib, pazopanib, sorafenib, and of these, sunitinib was the only agent to induce short-term partial remissions in 13 % of patients with good tolerability in a phase II trial [51], but a second trial failed to confirm the activity of sunitinib [52]. Pazopanib and sorafenib only induced tumor marker declines in 80 and 44 % of patients in small phase II trials without any objective responses [53, 54]. Another TKI targeting VEGFR, PDGFR and FGFR, nintedanib has shown promising activity in GCTs in vitro [55], but no clinical trial has been initiated to date. Furthermore, the antiparasitic drug suramin also targets PDGFR and fibroblast growth

Table 2 Ongoing clinical trials for refractory GCTs

Agent/regimen	Principal investigator	Estimated enrollment	Status	NCT trial number
Conventional chemotherapeutic drugs				
Cabazitaxel	Fizazi K	34	Recruiting	NCT02115165
Cabazitaxel	Oldenburg J	29	Recruiting	NCT02478502
Molecularly targeted drugs				
Atezolizumab (MPDL3280A)	Hoffman-La Roche	250[a]	Recruiting	NCT02458638
BBI608 plus Paclitaxel	Boston Biomedical Inc.	390[a]	Recruiting	NCT01325441
Brentuximab-Vedotin	Necchi A	24	Recruiting	NCT01851200
	Jospehson N	84[a]	Completed, no data published	NCT01461538
Dabrafenib plus Trametinib	GlaxoSmithKline	135[a]	Recruiting	NCT02034110
Everolimus	Fenner M	25	Completed, no data published	NCT01242631
LEE011	Novartis Pharmaceuticals	90[a]	Recruiting	NCT02187783
Olaparib	De Giorgi U	29	Recruiting	NCT02533765
Pembrolizumab	Hanna N	20	Recruiting	NCT02499952
Sirolimus plus Erlotinib	Laetsch T	11	Recruiting	NCT01962896

Information collected from www.clinicatrials.gov accessed at 06-15-2016

[a] These trials recruit patients with solid malignancies including refractory GCT patients

factor receptor (FGFR) and had promising antitumor activity in vitro, but failed to induce clinical responses in a phase II trial [56].

Targeting of BRAF-mutated disease As described previously, a significant proportion of refractory GCTs may harbor the oncogenic *BRAF* V600E mutation. BRAF inhibitor vemurafenib has not been tested in GCTs, but a currently recruiting phase II trial is investigating the double inhibition of MAPK pathway proteins BRAF and MEK by dabrafenib and trametinib in *BRAF* V600E-mutated rare cancers (NCT02034110).

Targeting of mammalian target of rapamycin Targeting mTOR for anti-cancer treatment is an essential approach in renal cell carcinoma, for example. The selective mTOR inhibitor everolimus has been evaluated in two phase II trials in refractory GCT patients. Results of one trial have been published to date, yielding a disappointing activity with no objective responses and only 6 out of 15 patients achieving 12-week progression-free survival [57]. Therefore, mTOR inhibition does not seem to substantially benefit refractory GCT patients' survival.

Targeting cancer-specific cell surface structures Embryonal carcinomas, as well as Hodgkin's lymphomas and anaplastic large cell lymphomas, are characterized histopathologically by expression of CD30. The antibody–drug conjugate brentuximab-vedotin consists of the cytotoxic agent monomethyl auristatin E linked to the chimeric monoclonal anti-CD30 antibody vedotin and was approved for the treatment of relapsed Hodgkin's lymphoma in 2011. Currently, this antibody is investigated in phase II trial in refractory CD30-positive GCT patients (NCT01851200). Preliminary data of a first interim analysis of nine patients in this phase II trial revealed a promising response rate of 22 % (one complete and one partial remission) and tumor marker responses in 78 % of patients after the first cycle and 44 % after the second cycle, but responses were only very short-lived with a progression-free rate of 11 % after 3 months, only [58]. Potential reasons for the limited durability of responses remain open, yet.

Checkpoint-inhibition A first trial investigating anti-PD-1-antibody pembrolizumab in platinum-refractory disease has been initiated at Indiana University, but recruitment has not started yet (NCT02499952). In another trial, GCT patients will be evaluated as part of different solid tumor entities in an open-label phase II trial of anti-PD-L1-antibody atezolizumab (NCT02458638). Thus, the potential of checkpoint-inhibition in GCTs remains to be elucidated. Ongoing clinical trials in refractory GCT patients are listed in Table 2.

Role of surgery

Surgical resection of post-chemotherapy residual masses is recommended particularly for non-seminomatous GCTs owing to the chemo-resistant nature of teratoma, which might be present in mixed non-seminomas. After salvage chemotherapy, vital carcinoma and/or teratoma can be found in about 40–70 % of patients [59–61]. Therefore,

resection of all residues ≥1 cm is strongly recommended in non-seminoma, if technically feasible [62]. As described in the GOP phase II GTCSG trial and the retrospective series of Necchi et al., patients achieving NED status by multimodal treatment have a substantially improved survival [10, 17].

Upfront surgical salvage approaches may be an option for selected patients with chemo-refractory disease and tumor marker elevations despite intensive pretreatment, if all manifestations are considered to be resectable. Some studies reported long-term disease-free survival in this clinically challenging situation in 21–50 % [63–66]. Whenever considered, this so-called 'desperation surgery' seems to be more reasonable in patients with AFP elevations rather than with rising ßHCG values. However, such surgical treatment should only be applied in expert uro-oncological centers after interdisciplinary discussion [64, 66].

Conclusions

Long-term survival after failure of cisplatin-based combination chemotherapy and/or high-dose chemotherapy is scarce. To date, the most effective treatment option so far is the triple-combination of gemcitabine, oxaliplatin and paclitaxel (GOP). In combination with subsequent resection of all residual masses, long-term survival may be achieved in about 10 % of patients [11]. Resection of residual masses is paramount since viable tumor was found in 67 % of patients, who underwent secondary resection [10].

Apart from combination chemotherapy, data on effectiveness of single-agent or combination systemic treatment after failure of GOP are lacking. Whenever single-agent palliative treatment is considered, oral etoposide may be a well tolerable option, but response rates are expected to be low [67]. Salvage surgery without prior systemic treatment despite rising tumor marker levels may be curative for selected, chemo-refractory patients, but only if resection of all visible manifestations is technically feasible [64].

Therefore, new treatment options are urgently needed to improve outcomes in this rare clinical setting. Based on reasonable activity in vitro, several targeted agents have been investigated in non-selected phase II trials with overall disappointing results. These include tyrosine kinase inhibitors, such as sunitinib, pazopanib, sorafenib, imatinib mesylate, tivantinib and anti-angiogenic agents, i.e., thalidomide and lenalidomide [13]. If combined treatment with targeted agents plus conventional chemotherapy may hold promise, remains to be elucidated. Emerging immunomodulatory treatments with checkpoint inhibitors targeting the PD-1/PD-L1-axis in refractory GCTs are currently under investigation, i.e., pembrolizumab (NCT02499952) and atezolizumab (NCT0245638).

Authors' contribution C Oing was involved in project development, data collection, data analysis and manuscript writing/editing. WH Alsdorf collected data, analyzed data, and wrote and edited the manuscript. G von Amsberg was involved in project development and manuscript writing/editing. K Oechsle was involved in data analysis and manuscript writing/editing. C Bokemeyer developed the project, and wrote and edited the manuscript.

Compliance with ethical standards

Conflict of interest All authors herewith declare that there is no financial or non-financial conflict of interest to bias the development of this manuscript.

Ethical standard As this project is solely a review of the literature, no primary research involving human participants has been conducted, and accordance of the literature included in the manuscript with accepted ethical guidelines has been assumed.

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