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Targeted therapies in the treatment of germ cell tumors: The need for new approaches against "orphan" tumors

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Contents

Abstract

Germ cell tumors (GCTs) are a heterogeneous group of tumors that are highly clinically relevant to oncologists. GCTs are generally highly sensitive to cisplatin-based chemotherapy and represent a model for curable neoplasms. Cisplatin-based combination therapy followed by surgical resection of the residual tumor is the cornerstone for GCTs treatment.

Although the overall cure rate is high for patients with GCTs, patients with a poor prognosis according to International Consensus Criteria or with chemoresistant disease remain a major clinical challenge. Currently, between 15% and 20% of patients with metastatic disease still progress and will die as a consequence of the disease. Therefore, the discovery of new treatment strategies or new drugs based on translational oncology remains a priority for the treatment of patients with cisplatin-refractory disease and those with a poor prognosis. Clinical trials with new targeted therapies are ongoing for the treatment of GCTs. In this article, we review some of the new targeted biologic therapies that act on the most relevant oncogenesis pathways and are in clinical development for the treatment of GCTs.

Key words: Targeted therapy; Germ cell tumors; Testicular tumors

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1. Introduction

Germ cell tumors (GCTs) are a heterogeneous group of tumors that are highly clinically relevant to oncologists. These tumors comprise only approximately 1% of all human neoplasms, but they are the most common solid malignancies in young men aged between 20 and 35 years. Advanced GCTs are classified according to International Consensus Criteria using serum tumor marker values, the site of metastasis, histology, and the primary site, leading to risk-directed therapy as the standard treatment approach [1]. GCTs are generally highly sensitive to chemotherapy and represent a model for curable neoplasms. Cisplatin-based combination therapy followed by surgical resection of the residual tumor is the cornerstone of GCTs treatment [2]. Approximately 75% of patients with disseminated disease have a complete response to initial chemotherapy, and of the remaining 25% who do not respond, 50% have a complete response to second-line salvage (cisplatin, ifosfamide, and either vinblastine or paclitaxel) or high-dose chemotherapy. Despite these remarkable results, between 15% and 20% of patients with metastatic disease, mainly those in the poor risk group according to International Consensus Criteria, still progress and will die as a consequence of the disease [3]. Clinical investigations have attempted to improve the outcomes of these patients using different strategies, such as doubling the dose of cisplatin, substituting ifosfamide for bleomycin, using maintenance chemotherapy, and using a dose-intensive sequential chemotherapy regimen. However, none of these patients has shown an improvement in survival compared with standard therapy using cisplatin, bleomycin and etoposide (BEP) [4]. No practical progress has therefore been made in this clinical condition since the advent of the use of BEP for 4 cycles. Only the experience of the treating physicians and the institution improved the outcomes of patients with poor-prognosis GCTs [5]. Therefore, the discovery of new treatment strategies or new drugs based on translational oncology for patients with cisplatin-refractory disease or those with a poor prognosis remains a priority. The crucial question is how we can more effectively design new treatments and treatment strategies? To answer this question, medical oncologists and researchers should work on improving our knowledge of factors that influence chemotherapy resistance and on increasing our understanding of the biological factors that may lead to the development of targeted therapies for chemotherapy-resistant disease. In this article, we review some of the new targeted biologic therapies that act on the most relevant oncogenesis pathways and that are in clinical development for the treatment of GCTs.

2. Targeting the HER receptor family

The epidermal growth factor receptor (EGFR) family consists of 4 members: HER1 (also known as the epidermal growth factor receptor, EGFR), HER2, HER3 and HER4. All of these EGFR family members are closely related. The protein structure of EGFR family members is composed of an intracellular tyrosine kinase (TK) domain, a transmembrane domain, and an extracellular domain that binds to a ligand (except for HER2, for which no natural ligands have been identified and which is activated through the establishment of a heterodimer with other EGFR family members). The binding of a ligand to the extracellular domain of the receptor results in the phosphorylation of various factors and thereby activates several intracellular signal transduction pathways, which involve ras/raf-1/mitogen-activated protein kinase, phosphatidylinositol-3 kinase (PI3K) and C phospholipase. These signaling cascades lead to the transcription of genes responsible for cellular proliferation, differentiation, angiogenesis and survival.

2.1. HER1 (EGFR) inhibition

EGFR is overexpressed in many epithelial tumors and is one of the main anticancer drug targets for some of these tumors, such as head and neck, lung and colon tumors. Between 24% and 65% of non-seminoma tumors show EGFR expression, particularly in pure choriocarcinomas or in the choriocarcinoma component of mixed forms. In one study, EGFR expression was studied in 182 GCTs. No EGFR reactivity was detected in 44 seminomas or 32 yolk sac tumors, whereas 20/28 teratomas and all 7 choriocarcinomas expressed EGFR [6]. In another study, strong EGFR expression was detected in 16/24 testicular tumors only in the β-human chorionic gonadotrophin-positive tumor components [7]. Durán et al. [8] studied EGFR expression in 109 histological samples from 84 patients with GCTs. The most frequently found histological type was choriocarcinoma (86%), as detected by staining for this marker. However, there was no relationship shown between EGFR expression and patient outcome in either predictive or prognostic terms. There are no available data on the mutational status of EGFR expression in GCTs. A phase II study of gefitinib in patients with chemo-refractory GCTs expressing EGFR (Indiana University) is being conducted; the study is complete, but the data have not been published yet.

2.2. HER2 inhibition

Her2/neu is an epidermal growth factor receptor that has been shown to be expressed on the cell surface of approximately 25–30% of breast cancers and many other epithelial malignancies. Frequently, the expression of Her2-neu correlates with poor prognosis for patients with breast cancer, but it does not have prognostic relevance for patients with other malignancies.

Between 12 and 25% of GCTs overexpress Her2, mainly in choriocarcinomas and the differentiated teratomatous component of non-seminoma tumors [9]. However, amplification of this gene, as observed by using fluorescence in situ hybridization, is rare, being found in only 3% of cases. This

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Table 1
Studies using imatinib for the treatment of GCTs.

Study	Design	Previous treatments	Efficacy
Einhorn et al. [20]	Phase II Imatinib 600 mg/d $n = 6$ pts c-Kit + IHQ of 18 evaluated. Not evaluated mutations	Refractory	0 RR 1 SD for 3 months with > 50% drop α-FP
Piulats et al. [21]	Phase II Imatinib 400 mg/d $n = 7$ pts c-Kit + IHQ	Refractory	0 RR
Pedersini et al. [22]	Case report of 1 seminoma c-kit + IHQ Imatinib 400 mg/d	Refractory	1 CR with DFS > 24 months
Pectasides et al. [23]	Case report of 1 seminoma Imatinib 400 mg/d + paclitaxel, oxaliplatin and gemcitabine	Resistant	1 CR with DSF > 32 months

RR, response rate; SD, stable disease; CR, complete response; DFS, disease-free survival; IHQ, immunohistochemistry; pts: patients.

finding makes Her-2/neu seem irrelevant as a therapeutic target for GCTs [10]. Trastuzumab is a humanized monoclonal antibody against the extracellular domain of Her2. The only clinical data for trastuzumab used for the treatment of GCTs is a case report of a heavily pretreated cisplatin-refractory tumor overexpressing HER2/neu in a resected lung metastasis. After initial treatment with standard doses of trastuzumab, there was a transient decrease in the serum alpha-fetoprotein level for ten weeks [11].

3. c-KIT/stem cell factor pathway

The proto-oncogene c-kit encodes a transmembrane tyrosine kinase receptor that binds to its ligand, stem cell factor (SCF). The c-kit/SCF pathway is crucial for testicular embryonic development and spermatogenesis [12]. Additionally, c-kit is expressed in GCTs; it is almost restricted to seminoma tumors being expressed in 90–100% of these tumors and is expressed in only 7–32% of non-seminoma tumors [7,13,14].

Imatinib was primarily designed to inhibit bcr-abl activity and to treat chronic myeloid leukemia. However, imatinib is also an inhibitor of c-kit tyrosine kinase activity and it is the treatment of choice for metastatic gastrointestinal stromal tumors (GIST), which frequently express constitutively activated forms of c-kit. Activating mutations of c-kit are most commonly associated with tumors arising from cells whose development depends on an intact c-kit/SCF pathway; these tumors are most frequently GIST and mastocytomas. Unlike GIST, somatic mutations are relatively rare in GCTs, with a higher frequency in seminoma tumors (1–25%) [15]. These mutations have been found in 93% of bilateral GCTs but only 2% of unilateral tumors [16]. The most commonly found mutation is in exon 17 (D816H), and there is a less common mutation in exon 11 [17]. However, the growth of tumors that carry the exon 17 mutation is not inhibited by imatinib [18,19].

Two phase II studies have been conducted to determine the activity of imatinib in heavily pretreated patients with c-kit positive metastatic GCTs (Table 1). Einhorn et al. [20] screened 18 cisplatin refractory patients for c-kit expression by using immunohistochemistry, and they found only 6 patients (33%) with c-kit positive tumors. These patients were treated with imatinib at 600 mg/day orally, and no remission, either complete or partial, was observed. Five of the 6 patients had progressive disease, and only 1 of the 6 patients achieved stable disease, with $a > 50\%$ decline in serum alpha-fetoprotein for 3 months before progressing further. Piulats et al. [21] administered imatinib at a dose of 400 mg/day continuously to 7 patients with c-kit positive tumors as detected by immunohistochemistry. This study was halted early because of the lack of activity observed. Thus, in both of these small studies there was no evidence of imatinib activity in patients with c-kit positive refractory GCTs. This lack of activity can be related to the finding that the most frequently observed mutations in GCTs are in the kinase domain of c-kit, which is less sensitive to imatinib.

By contrast, two clinical cases of patients with refractory GCTs who were treated with imatinib have been reported. Pedersini et al. [22] reported a patient with refractory seminoma with c-kit positive expression, as detected by immunohistochemistry, who was treated with imatinib alone at 400 mg daily. The tumor's c-kit mutation status was not determined. After 3 months of treatment, there was a complete remission, and after 24 months of the treatment, the patient remained free of disease. Pectasides et al. [23] reported the case of a patient with a resistant seminoma tumor overexpressing c-kit, as detected by immunohistochemistry, who was treated with imatinib (400 mg/day) and intensive chemotherapy (paclitaxel, oxaliplatin and gemcitabine) and who achieved a complete remission. Whether the chemotherapy, imatinib, or both led to the complete remission of this disease is unclear.

4. Antiangiogenic agents

Angiogenesis is the development of new blood vessels. This complex process rarely occurs in healthy adult tissues, but it is a key factor in continuous tumor growth and the

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Table 2
Studies using bevacizumab for the treatment of GCTs.

Study	Design	Previous treatments	Efficacy
Voigt et al. [31]	1 case report choriocarcinoma + embryonal carcinoma HD-ICE + Bevacizumab 7.5 mg/kg every 3 wks	Refractory 3 lines CH previous	PR TTP 5 months
Mego et al. [30]	1 case report Bevacizumab 10 mg/kg every 2 wks	Growing mature teratoma	SD TTP 6 months
Ramasubbaiah et al. [32]	Phase II Oxaliplatin 85 mg/m^2 + bevacizumab 10 mg/kg every 2 wks $n = 18$	Relapsed or refractory median 3 lines (2–6) 8 prior HDCH 8 late relapse	Serologic response ($n = 16$): 3 CR (17%) and 3 PR (17%) RECIST response: 1 PR (6%)

RR, response rate; SD, stable disease; CR, complete response; PR, partial response; TTP, time to progression; HD-ICE, high dose ifosfamide etoposide and carboplatin; CH, chemotherapy.

development of metastases. Vascular endothelial growth factor (VEGF) is an angiogenic factor essential for embryonic and immediate postnatal development. In adults, VEGF functions are limited to injury repair and follicle formation. The VEGF receptors on the cell surface are almost exclusively expressed by endothelial cells. VEGF stimulates the proliferation, migration, and survival of endothelial cells, increases vascular permeability, and inhibits apoptosis. Processes intimately related to cancer, including hypoxia, the expression of oncogenes, and the abnormal expression of growth factors, may initiate the expression of VEGF genes. In most cancers, there is an increase in VEGF expression, which is associated with a poor prognosis. Thus, VEGF is a key mediator of tumor angiogenesis and constitutes an important target for the development of new angiogenesis-oriented therapies.

In GCTs, the study of angiogenesis seems to be an interesting approach. Several characteristics of GCTs suggest that angiogenesis has a role in their biological function. First, microvessel density (MVD), an indirect measure of neoangiogenesis, may be predictive of the presence of lymph node metastases in localized GCTs [24]. In a study that included 51 localized GCTs, the presence of teratomas and seminomas was correlated with higher MVD and higher levels of VEGF, as measured by immunohistochemical analysis, than in normal testicular tissue. These differences between the tumor tissue and normal tissue suggest that angiogenesis is somehow related to the presence of tumor tissue in the testis [25]. Two other studies have also shown higher MVD and VEGF levels in tumor tissue than in normal testicular tissue [27,28], with one of these studies showing that these two parameters have a potential predictive value for the development of metastasis [28]. Second, patients with GCTs tumors have high serum levels of proangiogenic factors (VEGF, FGF and PDGF) compared with the normal population [28,29]. Third, VEGF and/or VEGF receptor (VEGFR) expression is associated with the development of metastases and poor prognosis in GCTs [24,27].

Bevacizumab is a humanized monoclonal IgG1 antibody that blocks the binding of all isoforms of VEGF to VEGFR, and it was the first antiangiogenic drug approved for the treatment of various metastatic solid tumors, such as colon, breast or lung tumors, in combination with chemotherapy. Bevacizumab has several toxic properties and can cause hypertension, proteinuria, thrombosis or bleeding, delayed healing, and gastrointestinal perforation or fistulae. Clinical experience with bevacizumab in the treatment of GCTs is very limited (Table 2). One patient with a growing mature teratoma showed stable disease during six months of treatment with bevacizumab as a monotherapy [30]. Another patient with a platinum refractory GCTs who was treated with bevacizumab plus a high dose of chemotherapy achieved a partial response with a progression-free survival time of 5 months [31]. The only phase II trial that has been reported for bevacizumab was conducted in combination with oxaliplatin in 18 patients diagnosed with refractory GCTs who had been heavily pretreated. Eighteen patients were evaluated for serologic responses, and there were 3 complete (17%) and 3 partial (17%) responses. Ten patients had measurable disease according to RECIST evaluation, and no complete responses were observed; only one patient had a partial response according to RECIST and serologic criteria (6%). This combination was well tolerated, but its activity was not significantly different from previous trials with oxaliplatin alone [32].

Recently Nitzsche et al. have identified novel compounds (HP-2 and HP-14) are able to potently block GCTs cell growth and decrease angiogenesis microvessel formation in vitro and in vivo. Both compounds may become new candidates for target therapy in GCTs treatment and warrant further evaluation [33].

5. Multitargeted tyrosine kinase inhibitors

Enhanced activity of many receptor tyrosine kinases (RTK) has been implicated in tumor growth, progression, metastasis and angiogenesis. Some of these RTKs, such as c-Kit, PDGFRs and VEGFRs, are implicated in the development of human testicular GCTs, [26,34,35], constituting a

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Table 3
Studies using sunitinib for the treatment of GCTs.

Study	Design	Previous treatments	Efficacy
Feldman et al. [37]	Phase II Sunitinib 50 mg/d 4 wks or 6 wks at 37.5 mg continuous $n = 10$ pts	Relapsed or refractory Median 3 lines (3–7) 30% mediastinum 80% HDCH	0 RR, 5 SD 4 mild tumor markers decline
Kollmannsberger et al. [38]	Phase II Sunitinib 50 mg/d 4 wks followed by a 2 wks break $n = 33$ pts	Relapsed or refractory Median 2 lines (1–6) 55% refractory 67% HDCH	ORR: 12% (4 PR) 13 pts SD of short duration (Median 2.34 months) PFS at 3 months 26

RR, response rate; SD, stable disease; CR, complete response; PR, partial response; PFS, progression-free survival; HDCH, high dose chemotherapy.

rationale for the simultaneous blockade of multiple targets or pathways.

Sunitinib is a multitargeted tyrosine kinase inhibitor that inhibits VEGFR, platelet-derived growth factor receptor, stem cell factor receptor (kit), and colony stimulation factor receptor-1. In a preclinical model, sunitinib as a single agent or combined with cisplatin showed antitumor activity against human testicular GCTs. More importantly, sunitinib inhibited the growth of cisplatin-resistant choriocarcinomas, suggesting that sunitinib might be a new alternative for the treatment of CDDP-refractory patients [36].

Two phase II studies have assessed the activity of sunitinib in patients with relapsed or refractory GCTs (Table 3). In a study by Feldman et al. [37], ten patients were enrolled. The first five patients received sunitinib at 50 mg daily for four weeks, followed by a two-week break. Because four patients treated with this schedule had a mild tumor marker decline during the fourth week and a subsequent rise of markers during the two-week break, the schedule was changed to 37.5 mg continuously for the next 5 patients. Marker stabilization was observed, but there were no objective responses; only 5 patients had stable disease. Only 1 patient required a dose reduction, owing to grade 3 mucositis. In a second study, Kollmannsberger et al. [38] administered 50 mg daily sunitinib for four weeks, followed by a two-week break, to 33 patients with multiply relapsed or cisplatin-refractory GCTs. Two confirmed partial responses were observed, as well as 2 unconfirmed partial responses, making the overall response rate 12%. Disease stabilization for a short duration was seen in 13 patients (median 2.34 months). The three-month progression-free survival rate was 26%; the six-month survival rate was 36%; and the 1-year survival rate was only 5%. The most frequent grade 3/4 toxicities were myelotoxicity, mucositis, and hand-foot syndrome, which occurred in 13 patients. Sunitinib as a monotherapy was well tolerated in both studies, but at standard doses, it showed a very modest activity against highly refractory GCTs.

6. Poly (ADP-ribose) polymerase inhibitors

The poly (ADP-ribose) polymerase (PARP) pathway comprises a family of enzymes participating in the repair of DNA abnormalities. The most abundant member is PARP-1, which is thought to play a key role in single-stranded DNA base-excision repair. PARP inhibition leads to an accumulation of single-strand DNA breaks and subsequent double-strand DNA breaks at replication forks. These breaks are normally repaired via the homologous recombination double-stranded DNA repair pathway, major components of which are the tumor suppressor proteins BRCA1 and BRCA2. The use of PARP pathway inhibitors would avoid the repairing of DNA abnormalities in tumor cells containing BRCA1 and BRCA2 gene mutations, thus maintaining the DNA injury in these cells, which would then be selectively destroyed.

Currently, the potential role of the PARP pathway in pathogenesis and its value as a prognostic or predictive marker in GCTs is unknown. In a preclinical model, PARP-1 deficiency induced the differentiation of embryonic stem cells into choriocarcinomatous human GCTs [39]; choriocarcinomas are associated with a high metastatic potential and a poor prognosis.

However, GCTs are highly sensitive to cisplatin, and PARP-1 is a key regulator of DNA damage repair processes, including those induced by the cytostatic factor cisplatin. Increasing PARP-1 activity is one mechanism by which tumor cells avoid the apoptosis caused by DNA-damaging agents; inhibitors of PARP-1 have the potential to improve cancer chemotherapy, including cisplatin-based therapy.

In a preclinical study, Guggenheim et al. studied the role of PARP proteins in mediating cisplatin cytotoxicity in several cell lines. NTera2, a testicular carcinoma cell line, was extremely sensitive to PARP-1 inhibitors [40]. However, the data are still very inconclusive, and further studies are needed.

7. Conclusions and future directions

GCTs have a high rate of curability with chemotherapy; however, compared with other tumors, they have been "orphan" solid tumors in the development of new target therapies. The new targeted therapies have been studied in a limited number of patients, the majority of whom are at advanced phases of their disease, with poor outcomes, and the results

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Table 4
Ongoing or recently completed clinical trials with targeted therapies for GCTs.

Protocol ID and reference	Drug	Status	Study group
NCT00453310 [41]	Sunitinib	Completed	Memorial Sloan-Kettering Cancer Center
NCT00912912 [42]	Sunitinib	Active, not recruiting	M.D. Anderson Cancer Center
NCT00371553 [43]	Sunitinib	Completed	British Columbia Cancer Agency
NCT00772694 [44]	Sorafenib	Recruiting	Foundation Wygrajmy Zdrowie
NCT00042952 [45]	Imatinib	Completed	Cancer and Leukemia Group B
NCT00198159 [46]	Gefitinib	Completed	Indiana University School of Medicine
NCT00393861 [47]	Oxaliplatin plus Bevacizumab	Recruiting	Indiana University
NCT00936936 [48]	Bevacizumab plus 2 cycles of high-dose CH	Recruiting	M.D. Anderson Cancer Center
NCT00957905 [49]	Alvocidib and Oxaliplatin with or without Fluorouracil and Leucovorin	Recruiting	Memorial Sloan-Kettering Cancer Center
NCT01242631 [50]	Everolimus	Recruiting	Hannover Medical School

obtained have been modest. Some clinical trials investigating the treatment of GCTs with new targeted therapies are ongoing (Table 4). Although the overall cure rate is high for GCTs, patients with a poor prognosis according to the International Consensus Criteria or those with chemo-resistant tumors remain a major clinical challenge. Increasing the understanding of GCTs tumor biology and developing large-scale collaborations will be necessary to study new targeted therapies with clinical and translational objectives.

Competing interests

The authors declare that they have no competing interests.

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Biographies

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