Systemic Therapy, Trials, and Future Directions for Chordoma of the Spine

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Abbreviations

CDK4/6	Cyclin-dependent kinases 4 and 6
CDKN2A	Cyclin-dependent kinase inhibitor 2A
DSS	Disease-specific survival
EGFR	Epidermal growth factor receptor
EZH2	Enhancer of zeste 2
FDA	Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
JAK	Janus kinase
KIT	Tyrosine-protein kinase KIT
LAG-3	Lymphocyte-activation gene 3
mTOR	Mammalian target of rapamycin
ORR	Overall response rate
OS	Overall survival
PD1	Programmed cell death protein 1
PDGFB	Platelet-derived growth factor β
PDGFR	Platelet-derived growth factor receptor
PDGFRA	Platelet-derived growth factor receptor α
PDGFRB	Platelet-derived growth factor receptor β
PD-L1	Program cell death ligand 1
PFS	Progression-free survival

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PI3K	Phosphoinositide-3-kinase (PI3K)
PR	Partial response
PRC2	Polycomb repressive complex 2
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
RB	Retinoblastoma
RTK(s)	Receptor tyrosine kinase(s)
SD	Stable disease
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
STAT	Signal transducer activator of transcription
SWI/SNF	Switch/sucrose non-fermentable
TBXT	T-box transcription factor T
TCR	T cell receptor
TKI(s)	Tyrosine kinase inhibitor(s)
VEGFR	Vascular endothelial growth factor receptor
VP-16	Etoposide

Introduction

Surgical resection and adjuvant radiation can lead to long-term disease control in many patients with chordoma [1]. However, gross total resection is not always technically feasible, and subtotal resection is associated with disease recurrence, possible tumor seeding, and development of metastatic disease [2, 3]. Five-year conditional disease-specific survival (DSS) for patients with localized chordoma is 83%; however, 5-year conditional DSS is only 71% for those with metastatic disease [4]. The use of cytotoxic chemotherapy has been proposed and tested as an option for the treatment of metastatic chordoma; however, there has been little evidence to date supporting its clinical efficacy [5]. Furthermore, the rarity of chordoma precludes the study of systemic therapies using large-scale, prospective trials. Nonetheless, data from genomic, epigenomic, and transcriptomic analyses, along with the study of the chordoma tumor-immune microenvironment, have identified a number of promising new treatment targets.

Cytotoxic Chemotherapy

Chordoma is considered unresponsive to cytotoxic chemotherapy, and there is no prospective data to support its clinical use. To date the only available clinical trial data is derived from a small phase II, prospective study by Chugh et al. studying this use of cytotoxic chemotherapy in patients with advanced chordoma. In this trial, the authors found that a regimen of the topoisomerase I inhibitor, rubitecan, in 15 patients with advanced chordoma was associated with moderate toxicity and little clinical benefit; only one patient had an objective response to treatment [6].

Multi-agent regimens have been described in a handful of case reports with varying degrees of reported success. In their report, Fleming et al. described complete remission in two patients with dedifferentiated sacral chordoma treated with neoadjuvant radiation, sacrectomy, and adjuvant systemic therapy. One patient was treated with ifosfamide, and the other was treated with a six-drug regimen including cisplatin, etoposide, vincristine, dacarbazine, cyclophosphamide, and doxorubicin [7]. Similarly, in a retrospective review of six pediatric patients with clival chordomas, Dhall et al. found the use of adjuvant ifosfamide and etoposide (VP-16) resulted in disease stability in two patients with a median follow-up of 9 years from diagnosis [8]. Ceruso et al. similarly documented both clinical and radiographic responses in a patient with advanced sacral chordoma that was treated with oral cyclophosphamide and prednisone given on a metronomic schedule (continuous administration of low doses of the active drugs) [9].

Despite these isolated case reports, there are no high-quality data to suggest that cytotoxic chemotherapy is an effective treatment for either conventional and chondroid chordoma. Thus, development of targeted and immune-based therapies has been a major focus of chordoma research.

Molecular-Targeted Therapies: Receptor Tyrosine Kinases and Cell Signaling Pathways

Given the lack of demonstrated efficacy for conventional cytotoxic chemotherapy, there has been a drive to identify the key molecular changes associated with chordoma oncogenesis. Identification of the mutated or overexpressed genes and dysregulated molecular pathways has provided opportunities for the use of targeted therapies in the treatment of chordoma [10, 11]. Key changes that have been associated with chordoma tumorigenesis include increased expression and activation of receptor tyrosine kinases (RTKs) and alterations in both the downstream effectors of these RTKs and the negative regulators of RTK signaling [12, 13]. While no single, dominant molecular pathway has been implicated in the development of chordoma, analysis of patient chordoma samples has noted increased expression of the following RTKs: epidermal growth factor receptor (EGFR), tyrosine-protein kinase KIT (KIT), platelet-derived growth factor receptors A and B (PDGFRA and PDGFRB), and vascular endothelial growth factor receptor 2 (VEGFR2) [12, 14, 15].

Perhaps consistent with the relatively indolent growth pattern of chordomas, histopathology studies have found chordomas to have a relatively low burden of somatic mutations. Analysis of 37 chordoma tumor exomes or genomes revealed a median of 21 coding substitutions and 4 insertion-deletion mutations (indels) per case [16]. In spite of the relatively low mutation burden, alterations in a small number of pathways have been consistently identified. These include changes in the phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Noted changes include activating mutations in the PIK3CA gene and truncations or deletions in its negative regulator – phosphatase and tensin homolog on chromosome 10 (PTEN). Alterations in genes encoding regulators of the cell cycle have also been identified, including mutations in cyclin D/cyclin-dependent kinases

4 and 6 (CDK4/6), retinoblastoma (RB), and the Janus kinase (JAK)/signal transducer activator of transcription (STAT) pathways. All have been postulated to be involved in tumorigenesis [16–19].

Numerous preclinical studies support the use of targeted small molecule inhibitors in chordomas harboring alterations in these pathways among others. Clinical implementation of these therapies has been attempted with the use of several tyrosine kinase inhibitors (TKIs). TKIs that have been previously described in the preclinical or clinical setting include the PDGFR inhibitor imatinib; the KIT inhibitor dasatinib; the EGFR/ human epidermal growth factor receptor 2 (HER2) inhibitors erlotinib, lapatinib, and gefitinib; and the VEGFR inhibitors sorafenib, pazopanib, and sunitinib. Other inhibitors that have been described include the anti-EGFR antibody cetuximab and the PI3K/Akt/mTOR pathway inhibitors temsirolimus, sirolimus, and everolimus (Fig. 16.1) [10]. These pathways present targets for molecular therapies that have been evaluated in preclinical and, in some cases, clinical studies [10, 20]. A summary of phase II trials of TKIs for the treatment of chordoma is presented in Table 16.1.

PDGFR

Imatinib, a multi-kinase inhibitor with activity against BCR-ABL, KIT, and PDGFR, was the first molecular-targeted therapy to show clinical benefit in the treatment of chordoma. A phase II study of patients with advanced chordoma expressing platelet-derived growth factor β (PDGFB)/PDGF receptor β (PDGFRB) treated 56 patients with 800 mg/day of imatinib. While only one partial response (PR) was seen by at 6-month follow-up (ORR, 2%), 35 patients (70%) had stable disease (SD) for an overall clinical benefit rate of 64%. The median progression-free survival (PFS) and overall survival (OS) were 9.2 and 34.9 months, respectively [21]. Multiple other studies, including two other clinical trials, have investigated the use of imatinib, either as monotherapy or in combination with chemotherapy, in patients with chordoma [10, 22, 23].

Dasatinib, another PDGFR inhibitor that also has activity against Src, was studied in a phase II trial involving patients with locally advanced or metastatic sarcomas. Across the 32 included patients, median PFS was 6 months and OS was 43% and 18% at 2 and 5 years, respectively [24].

mTOR

Multiple clinical case reports have found mTOR inhibitors to have clinically significant activity against chordoma [25–27]. The combination of the mTOR inhibitor everolimus and imatinib was recently examined in a phase II clinical trial by Stacchiotti and colleagues. The examined cohort comprised 43 patients with advanced or metastatic chordoma that had progressed following initial surgical, radiation, or medical treatment. Of note, 13 patients had previously been treated with imatinib. While the antitumor effect was modest, with an ORR of 22.5%, 6 of

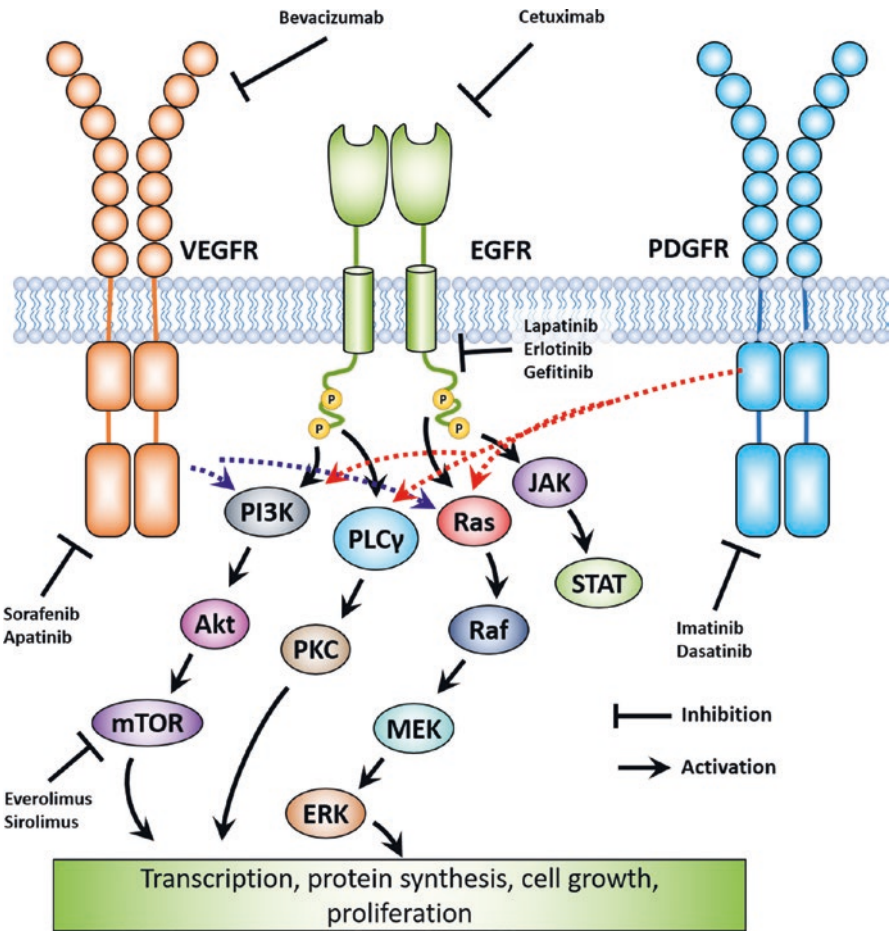

Fig. 16.1 Selected molecular-targeted therapies against RTK signaling pathways for the treatment of chordoma

30 chemotherapy-naïve patients (20%) and 3 of 13 patients (23%) previously treated with imatinib demonstrated a partial response, as defined by Choi criteria [28]. Molecular characterization of this subgroup found that these patients had tumors with high levels of mTOR phosphorylation (present in ≥60% of tumor cells). Similar phosphorylation levels were not observed in the tumors from patients who did not benefit from treatment with everolimus and imatinib [29].

VEGFR

VEGF protein expression is detected in chordoma samples [15, 30, 31]. Accordingly, multiple anti-VEGF therapies have been investigated for their clinical utility in patients with advanced or unresectable chordoma. Agents that have been previously

Table 16.1 Phase II clinical trials of TKIs for the treatment of chordoma. Median PFS and OS in months using RECIST 1.1 criteria are reported unless otherwise noted

Pathway targeted	Drug [trial reference]	Number of patients	PFS (months or otherwise noted)	OS (months or otherwise noted)	BORR (%)
PDGFR	Imatinib [21]	56	9.2	34.9	2
	Dasatinib [24]	32	6.3[a]	Not reported[b]	19[a]
mTOR	Everolimus + imatinib [29]	43	14	47.1	22.5
VEGFR	Sorafenib [38]	9	Not reported	Not reported	44[c]
	Sorafenib [39]	27	Not reached	Not reached	3.7
	Sorafenib [40]	26	72.9% at 9 months	86.5% at 12 months	Not reported
	Apatinib [41]	2	18	88% at 12 months	3.7
EGFR	Lapatinib [53]	18	8	25	33.3

Key: BORR best overall tumor response rate, *OS* overall survival, *PFS* progression-free survival
[a]Evaluated by Choi criteria
[b]Reported values not specific for patients with chordoma included in the study
[c]Includes patients with stable disease

examined include the small molecule VEGF inhibitors sorafenib [32], pazopanib [23, 33, 34], and sunitinib [23], as well as the humanized anti-VEGF-A antibody, bevacizumab [35], and thalidomide, which modulates VEGF expression [36, 37].

Of these, the small molecule inhibitors have been most popular, and to date there have been four phase II clinical trials examining the clinical utility of anti-VEGF TKIs in patients with chordoma [38–41]. Two trials [38, 39] evaluated the use of sorafenib, a VEGFR1/2/3 and PDGFRB inhibitor [42]. One of these trials, the phase II Angionext trial, included 26 patients with advanced chordoma who were treated with sorafenib at a dose of 800 mg/day. This treatment was associated with a 9-month PFS of 72.9% [39]. Sunitinib was similarly examined in a trial of advanced non-GIST soft tissue sarcomas, including nine patients with chordoma. Patients were treated with 37.5 mg of daily sunitinib and examinations at 16 and 24 weeks demonstrated stable disease in 44% and 22% of chordoma patients, respectively [40], as defined by RECIST criteria [43]. Finally, a single-arm, phase II nonrandomized trial of apatinib, a VEGFR-2 inhibitor, was performed at a single institution [41, 44]. The results suggested it may have mild efficacy on disease control. Although only one patient had a partial response by RECIST criteria, median PFS was 18 months, 1-year OS was 88%, and 63% of patients had local disease control at 6 months.

EGFR

The genes encoding EGFR and its ligands are highly expressed in patient-derived chordoma samples. Additionally, comparison of gene expression in fetal nucleus pulposus tissue and chordoma samples demonstrates significantly higher EGFR

protein expression in tumor sample [17, 45]. Inhibition of EGFR and other human epidermal growth receptor family members has therefore been an attractive strategy for the treatment of chordoma. Case reports have detailed the use of small molecule inhibitors of EGFR, including erlotinib and gefitinib, as well as the anti-EGFR chimeric monoclonal antibody, cetuximab. These case reports have suggested anti-EGFR treatments to have clinical benefit both in terms of tumor response and improvement in neurologic symptoms secondary to chordoma mass effect [35, 46–52].

Another small molecule EGFR inhibitor, lapatinib, has also been evaluated in a phase II clinical trial. In this trial, lapatinib, a dual EGFR and HER2 inhibitor, was administered to 18 patients with locally advanced or metastatic, EGFR-expressing chordoma at a dose of 1500 mg/day (mean dose intensity of 1282 mg/day). Six of the 18 patients (33%) experienced partial disease response (ORR 33.3%), and seven others had stable disease by RECIST criteria with a minimum follow-up of 6 months. Median PFS in the cohort was 8 months, and the overall clinical benefit rate was reported at 22% [53]. Based upon these promising initial results, Stacchiotti et al. have begun a phase II, single-arm trial of the second-generation EGFR TKI, afatinib. The trial is currently enrolling patients with locally advanced or metastatic EGFR-expressing chordoma (NCT03083678).

CDK4/6

Progression through the cell cycle is tightly controlled by a large network of proteins, and dysregulation of this cycle has been implicated in the tumorigenesis of multiple malignancies, including chordoma [54]. One key molecule is p16, encoded by the gene cyclin-dependent kinase inhibitor 2A (*CDKN2A*). p16 negatively regulates CDK4/6, which is responsible for stimulating cells to progress through the G1/S transition of the cell cycle [55]. CDK4/6 are often overactivated in chordoma samples due to loss of p16, resulting in increased cellular proliferation [56, 57]. Inhibition or downregulation of CDK4/6 may therefore represent a potential therapeutic target. Both strategies have proven effective in vitro, with CDK4/6 inhibition in p16-deleted cells resulting in decreased cellular proliferation and repression of other oncogenic properties [57, 58]. The CDK4/6 inhibitor used in these studies – palbociclib – is currently approved for the treatment of breast cancer [59] and is undergoing evaluation of its efficacy in a phase II study of patients with advanced or metastatic chordoma (NCT03110744).

Epigenetic Therapies

In the past decade, epigenetic regulation of chromatin structure and gene expression has been increasingly recognized as an important driver in tumorigenesis [60]. Control of chromatin packing dynamics is therefore another potential target for novel chordoma therapies. Missense and nonsense mutations in SMARCB1, a

member of the ATP-dependent SWI/SNF chromatin-remodeling complex, have been documented in chordoma samples [18]. Low expression of the SMARCB1 protein is additionally associated with poor prognosis in skull base chordomas [61]. SMARCB1 and the SWI/SNF complex play key roles in the epigenetic regulation of cell cycle progression and multiple signaling pathways [62]. Inactivation of SMARCB1, through either loss of protein expression or mutational inactivation, leads to increased activity of enhancer of zeste 2 (EZH2), a histone-lysine N-methyltransferase that forms the catalytic subunit of the polycomb repressive complex 2 (PRC2) [63, 64]. Increased PRC2 activity amplifies chromatin methylation, notably in regions encoding genes crucial to cell survival, proliferation, and invasion [65].

Curiosity about the efficacy of EZH2 inhibitors served as the basis of a phase I trial of tazemetostat, a selective EZH2 inhibitor [66]. In this trial of 46 patients with relapsed or refractory INI1-negative tumors, two children were being treated for chordoma. Though the chordoma cohort was too small to reach definitive conclusions, one of the chordoma patients was forced to withdraw from the study after experiencing worsening pain from her sacral mass. However, her tumor was found to be stable by RECIST 1.1 criteria at the time of discontinuation, and she experienced complete response of her pulmonary metastases. After withdrawing, she received radiation to the sacral mass, and radiographic follow-up at 4 months demonstrated persistent remission of her distant pulmonary metastases, suggesting that tazemetostat may induce an antitumor immune response [67]. This remains speculative though, and a phase II clinical trial is currently underway, which exams tazemetostat for the treatment of adult patients with SMARCB1-negative tumors, including poorly differentiated chordoma (NCT02601950).

Immunotherapy

The immune system and its impact on the development and treatment of cancer has been studied since the nineteenth century [68]. Work over the previous three decades has led to a more complete understanding of the role the immune system plays in the detection and elimination of neoplastic cells. This process of immune surveillance is regulated by multiple factors, including T cell immune checkpoints, molecular interactions that negatively regulate T cell function. For example, the programmed cell death-ligand 1 (PD-L1) found on cancer cell membranes binds to the programmed cell death protein 1 (PD-1) on CD8+ effector T cells resulting in CD8+ T cell anergy [69]. Disruption of this anergy-inducing interaction has therefore been a focus of novel immunotherapies and has stimulated the development of drugs that alter immunosurveillance by inhibiting these immune checkpoints. These checkpoint inhibitors are rapidly becoming a key aspect of chemotherapy as they have been successfully used to treat patients with cancers in which chemotherapy had been ineffective. Their use in the treatment of chordoma is therefore also the subject of great interest and study [5, 70].

The FDA has approved use of multiple antibodies that target components of two key immune checkpoint pathways: the binding of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to CD80/CD86 and the binding of PD-1 and PD-L1. These inhibitors include the anti-CTLA-4 antibody ipilimumab, the anti-PD-1 antibodies nivolumab and pembrolizumab, and the anti-PD-L1 antibodies atezolizumab, avelumab, and durvalumab [70]. Preclinical data has shown that chordoma cell lines express both PD-1 and PD-L1 at the gene and protein levels [71]. The chordoma tumor immune microenvironment may serve to increase the growth and invasive potential of chordoma cells. For instance, expression of the PD-L1 gene and protein is upregulated by exposure to pro-inflammatory cytokines such as IFN-γ [71]. Exposure to TNF-α also increases PD-L1 gene expression and upregulates expression of genes associated with the epithelial-mesenchymal transition, PI3K/AKT signaling, pro-angiogenesis, and anti-apoptotic pathways (Fig. 16.2) [72]. This suggests that chordomas may activate T cell checkpoints and decrease the activity of T cells in response to an otherwise immune stimulating environment.

Analysis of nine human chordoma tissue samples showed that 94.9% of the samples expressed PD-L1 as measured in a tissue microarray, and samples from patients with metastatic chordoma had higher expression of PD-L1 than those from patients with non-metastatic disease [73]. Infiltrating T lymphocytes (TILs) have also been examined. One study showing that 22% of TILs found in chordoma samples expressed PD-1, and a second observed detectable CTLA-4 on the majority of TILs in chordoma patient samples [74, 75]. Furthermore, treatment with avelumab, an anti-PD-L1 antibody, increased the immune-mediated killing of human-derived chordoma cell lines in vitro [76]. Taken together, these studies serve as rationale for targeting the immune system in the treatment of chordoma.

Recent case reports have shown that treatment with anti-PD-1 antibodies, such as pembrolizumab or nivolumab, led to reduction in tumor sizes and subjective clinical improvement. Notably, these improvements were observed even in patients with chordoma that was refractory to multiple earlier lines of therapy [77]. Both phase I and II clinical trials evaluating the use of anti-PD-1 antibodies alone, in conjunction with radiation or in combination with an inhibitor of another immune checkpoint, lymphocyte-activation gene 3 (LAG-3), are recruiting patients with chordoma (NCT03173950, NCT02989636, and NCT03623854).

Despite this, recent data has suggested that only a subset of patients with chordoma may be amenable to immunotherapy with checkpoint inhibitors. In order to be eliminated by the host immune system, tumor cells must not only downregulate anergy-inducing checkpoint molecules, but they must also actively express peptides novel peptides demonstrating them to be "non-self." This presentation is done through the interaction of human leukocyte antigen (HLA) class 1-peptide complexes on tumor cells and surface receptors on CD8+ effector T cells. Recently, Patel et al. [78] examined samples for surgically treated chordoma patients and found that 40% or more of chordoma samples may not express HLA class 1/peptide complexes. However, in vitro work has found proton- and photon-based radiation to increase HLA expression [79]. Consequently, paired radiotherapy and checkpoint

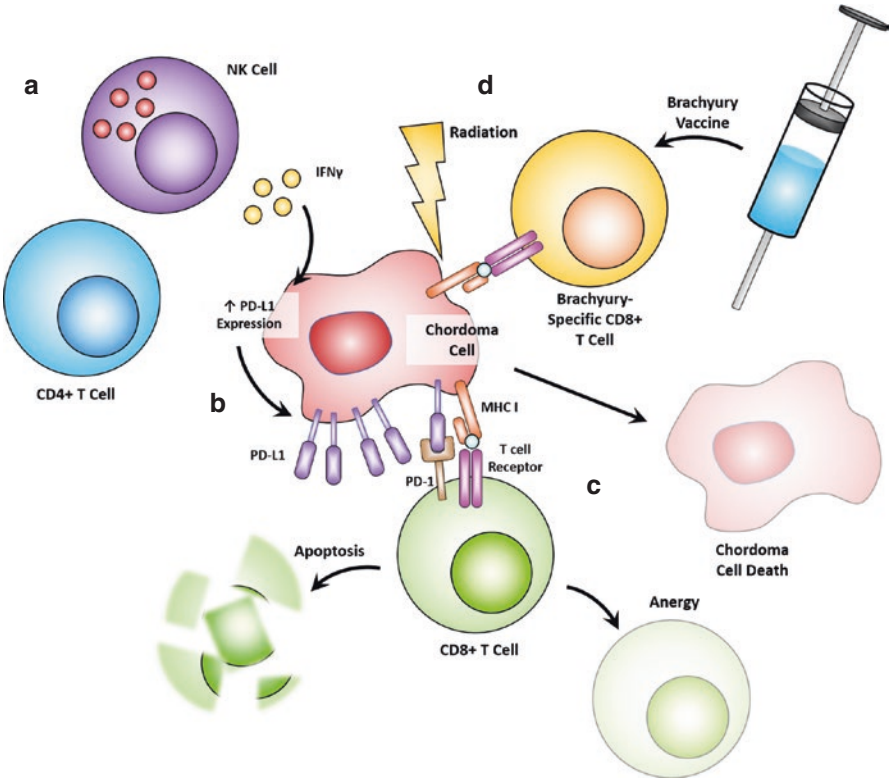

Fig. 16.2 The chordoma tumor immune microenvironment. (**a**) In response to pro-inflammatory signals and cytokines such as INF-γ, chordoma cells increase expression of PD-L1. (**b**) Higher levels of PDL-1 expression lead to activation of T cell immune checkpoints through binding to PD-1 receptors on the T cell surface. (**c**) Activation of T cell immune checkpoints induces T cell anergy to tumor-specific antigens and apoptosis of effector T cells. (**d**) Brachyury vaccine strategies use epitopes from brachyury-derived tumor antigens to induce production and activation of brachyury antigen-specific CD8+ T cells. These T cells have an enhanced ability to recognize and possibly destroy chordoma cells. Clinical trials of brachyury vaccines have also incorporated the use of radiation with the goal of enhancing the anti-tumor immune response

inhibitor administration may improve tumor cell killing. This is currently undergoing investigation in a phase I trial (NCT02989636).

Brachyury

Brachyury is a transcription factor encoded by the T-box transcription factor T gene (*TBXT*) located on the long arm of chromosome 6 [80]. Brachyury has a conserved role in development [81], and its expression has been established as a diagnostic marker in chordoma [82, 83]. Brachyury is highly expressed in patient chordoma samples, with the rare exception of a subset of dedifferentiated chordomas [84].

Chromosome 6 duplication and *TBXT* copy number gain have both been observed in chordoma cell lines and patient samples. The increased somatic copy number gain of *TBXT* has in turn been correlated with increased brachyury expression [85–88].

Preclinical studies have shown that brachyury is involved in numerous critical cellular pathways. These include pathways regulating cell growth, apoptosis, the epithelial-to-mesenchymal transition, and cellular differentiation [89–92]. In vivo experimental models have been used to demonstrate that disruption of brachyury expression or activity can prevent the formation of chordoma tumors or decrease the size of existing tumors [90, 92].

Based upon this preclinical evidence, brachyury has also become as an attractive target for systemic therapies. One such therapy is the chordoma Brachyury vaccine, originally described by Hamilton et al. in a murine model of metastatic colorectal adenocarcinoma [93]. The group found that treating mice transplanted with MC38 cells using a *Saccharomyces cerevisiae*-based brachyury vaccine produced robust brachyury-specific CD4+ and CD8+ T cell responses with minimal toxicity. Importantly, treated mice also showed a significant reduction in their lung metastasis burden. Based upon this, a phase I clinical trial of a yeast-based cancer Brachyury vaccine was launched in patients with chordoma or other advanced solid tumors (Fig. 16.2) [94]. The vaccine was well tolerated and induced the development or enhancement of brachyury-specific CD4+ and/or CD8+ T cells in 55% of patients. Of the ten patients with chordoma, none had evidence of disease progression at 5-month evaluation. Among these patients, the median PFS was 8.3 months, though only two patients had disease response (one with partial response and one with mixed response). Of note, both patients demonstrating disease response had received radiation treatment prior to their vaccination. This radiotherapy may have upregulated HLA class 1/brachyury complex expression, enhancing the "non-self" signal provided by the chordoma cells. Based upon this, two phase II trials have been initiated looking at concomitant treatment with radiotherapy and a Brachyury vaccine. One trial is examining patients with locally advanced, unresectable chordoma using concomitant radiotherapy and vaccination with the yeast-based Brachyury vaccine (NCT02383498) [95]. The second (NCT03595228) is using a poxvirus-based Brachyury vaccine (BN-Brachyury vaccine) with radiation in patients with chordoma. In this second study, the vaccine consists of two recombinant poxvirus vectors delivered in tandem as a prime-boost strategy. These viruses are modified to express brachyury as well as viral molecules known to increase immune cell activation [96].

Conclusions

Treatment of chordoma after exhaustion of local therapy options remains challenging. Chordoma has no established standard of care therapy with conventional cytotoxic chemotherapy proving ineffective. Large randomized trials of systemic therapy are difficult to conduct owing to the rarity of chordoma, the heterogeneous

nature of the disease, and the varying rates of progression observed across patients. Nevertheless, an enhanced understanding of the molecular drivers and tumor immune microenvironment in chordoma has opened the door for new, targeted treatment paradigms which may prove useful in long-term control or remission for those with advanced disease. Early results have been promising, but continued study is necessary, and the ultimate solution may rely on establishment of patient-specific regimens dictated by each tumor's unique genetic fingerprint.

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