27 Neurological Complications of Targeted Therapies

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27.1 Introduction

Neurotoxicity secondary to cancer-directed therapies is a widely recognized phenomenon in the treatment of patients with solid and hematologic malignancies. As there has been more recent use of targeted agents, early and timely recognition of rare but potential severe adverse neurologic effect will be critical, as this may limit the treatment course [1]. Toxicity may be the result of direct effects upon the nervous system, such as with chemotherapy-induced peripheral neuropathy, while there are also indirect effects to consider, which may occur due to metabolic or toxic factors produced by therapy. Early recognition is essential, particularly as the development of novel therapies has led to rapid adoption of these therapies as standard of care. As many of the agents and modalities discussed in this section have been established as treatments in systemic cancers, many are currently in use for central nervous system metastases or are under investigation, thus requiring more attention in distinguishing the effect of treatment from progressive intracranial disease.

27.1.1 EGFR

Epidermal growth factor receptor (EGFR) is part of the erbB family, encoded by erbB-1 (HER1), erbB-2 (HER2), erbB-3 (HER3), and erbB-4 (HER4), and is frequently overexpressed in non-small cell lung cancer (NSCLC) [2–4]. EGFR overexpression is found most commonly in adenocarcinoma histology and has been associated most frequently with women, those of East Asian descent, and non-smokers [5]. Over the past decade, collective understanding of the prognostic significance of EGFR in NSCLC has evolved, with advances in molecular profiling and characterization leading to the development of agents targeting EGFR. Use of EGFR tyrosine kinase inhibitors (TKI) now represents the standard of care for treatment of patients with NSCLC and activations mutations in EGFR [6]. In EGFR-mutated patients, initiation of EGFR TKIs in the newly diagnosed setting has led to prolonged progression-free (PFS) when compared to chemotherapy [7–10]. The later-generation EGFR TKIs have continued to demonstrate survival benefit in comparison to chemotherapy, both in local and metastatic NSCLC, notably osimertinib, given its demonstrated CNS activity [11].

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27.1.2 Gefitinib

Gefitinib was the first EGFR TKI to be approved as a monotherapy for patients with previously treated NSCLC. In the phase III IPASS trial, patients with EGFR-mutated NSCLC were randomized to either gefitinib or carboplatin/paclitaxel in the frontline setting [8]. While neurotoxicity was observed in the gefitinib-treated cohort in 66 patients (10.9%), 69.9% of patients randomized to the carboplatin-paclitaxel arm noted neurotoxic adverse effects [12]. Although prospective trials have shown activity of gefitinib in brain metastases from NSCLC, osimertinib remains the preferred agent in this setting [13].

Ocular side effects, specifically visual disturbances, were observed in two phase II trials in which patients with advanced NSCLC were treated with gefitinib. These were primarily described as blurred vision, photophobia, and bilateral hemianopia; however, it was not felt that gefitinib was associated with these adverse effects [14].

27.1.3 Erlotinib

Erlotinib is a first-generation EGFR TKI first approved in 2004 for second-line monotherapy in treatment of patients with locally advanced or metastatic NSCLC, following initial treatment with chemotherapy [15]. In patients with EGFR-mutated NSCLC brain metastases, erlotinib was shown to delay time to intracranial disease progression as well as overall survival in comparison to EGFR wild-type disease [16]. Regarding associated toxicity, in the phase III EURTAC trial which led to the approval of erlotinib as a first-line agent, the predominant drug-related adverse effects were non-neurologic, namely, fatigue, rash, and diarrhea. Among the 84 patients who were randomized to erlotinib, 8 (9%) reported neuropathy, as compared to 12 of 82 patients receiving standard chemotherapy [7].

27.1.4 Afatinib

Afatinib is a second-generation, irreversible pan-EGFR TKI approved for initial therapy of patients with advanced EGFR-mutant NSCLC. In the combined analysis of the phase III trials LUX-LUNG 3 and LUX-LUNG 6, in which afatinib was compared to chemotherapy in first-line treatment, in patients with asymptomatic brain metastases, afatinib was associated with longer PFS [9, 17–19]. In comparison to the other EGFR TKIs, neurotoxicity is uncommon with afatinib in the LUX-LUNG trials [20].

27.1.5 Osimertinib

Osimertinib is a third-generation irreversible EGFR TKI which inhibits both EGFR TKI-sensitizing and EGFR T790 M resistance mutations [6]. It is favored as initial management for patients with synchronous presentation of systemic and CNS disease [6]. Similar to other EGFR TKIs, it is not active in EGFR wild-type disease. It has been used increasingly in the first-line setting for treatment of advanced EGFR-mutant NSCLC, having shown efficacy superior to other TKIs for first-line treatment of EFGR-mutated NSCLC [6]. In initial and salvage therapy, osimertinib has also demonstrated improvement in central nervous system (CNS) penetration as well as durable response rates [11, 21]. Neurologic adverse effects in the osimertinib arm included headache, back pain, and asthenia [11].

27.1.6 Cetuximab

Cetuximab is a chimeric mouse/human monoclonal antibody against EGFR frequently used in management of head and neck, as well as colorectal cancers [22]. In the study of cetuximab monotherapy for salvage treatment of advanced colorectal cancer, among the most frequently reported adverse effects included headaches [23]. Additionally, there have been case reports of cetuximab-associated chronic inflammatory demyelinating polyneuropathy (CIDP), though causality was not established [24]. Nonconvulsive status epilepticus in the setting of posterior reversible encephalopathy syndrome (PRES) secondary to cetuximab has also been reported [25].

27.2 ALK

Approximately 5% of NSCLCs harbor alterations in the anaplastic lymphoma kinase (ALK) gene [27]. An inversion in chromosome 2 resulting in the 5′ end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3′ end of the ALK gene results in the fusion oncogene EML4-ALK [28]. Like EGFR-mutated NSCLC, ALK-rearranged tumors are associated with specific clinical phenotypes including young age and never smokers, as well as adenocarcinoma histology [3]. ALK rearrangements are mutually exclusive of EGFR and KRAS mutations. Screening for ALK following histologic confirmation of NSCLC is essential, as ALK-rearranged tumors are sensitive to ALK TKIs, which have been established as first-line therapy for newly diagnosed ALK-rearranged NSCLC [29]. Alectinib and ceritinib, specifically, have gained FDA approval for treatment of brain metastases in both the newly diagnosed and pretreated settings [26, 27].

27.2.1 Crizotinib

Crizotinib is a first-generation ALK TKI and one of the earliest used in clinical settings. In patients with ALK-rearranged brain metastases, its use has declined secondary to improved outcomes noted with alectinib and ceritinib as well as to higher rates of CNS relapse which have been observed [28]. In a large phase III trial, PROFILE 1014, among the most common neurologic adverse effects identified in this trial include vision changes (73.1%), neuropathy (50%), headache (48%), and dizziness (44%) [29].

27.2.2 Alectinib

Alectinib is FDA approved for first-line therapy for patients with ALK-rearranged NSCLC and for patients who had progressed while previously on crizotinib. In at least three phase III studies, ALEX, J-ALEX, and ALESIA, alectinib was compared to crizotinib in untreated, ALK-rearranged NSCLC. In all three trials, alectinib was associated with either prolonged PFS or reduction in the risk of disease progression or death [30–32]. Alectinib has additionally been found to have improved CNS penetration, achieving high brain-to-plasma ratios, intracranial response rates, and delayed risk of CNS progression in patients with baseline brain metastases [32]. In the J-ALEX trial, neurologic toxicity including dysgeusia, headache, and dizziness was observed and, however, was either grade 1 or grade 2. Additionally, the frequency of these events was lower in the alectinib-treated arm in comparison to crizotinib [32].

27.2.3 Ceritinib

Ceritinib is a second-generation selective ALK TKI with established potency 20 times greater than crizotinib and FDA approved in the first-line setting for patients with advanced, ALK-rearranged NSCLC [33]. In ASCEND-4, a randomized phase III trial in which ceritinib was compared to standard chemotherapy (pemetrexed-platinum therapy), in patients with measurable brain metastases, ceritinib was associated with prolonged PFS and higher intracranial response rates [33]. Headache (16%) was the most commonly reported neurologic adverse effect [33].

27.2.4 Brigatinib

Brigatinib is a second-generation ALK inhibitor which has activity against both ALK and ROS1 mutations and which has been associated with prolonged PFS in patients with untreated, advanced ALK-rearranged NSCLC, when compared to crizotinib [34]. Additionally, brigatinib has also been shown to result in higher intracranial response rates in patients with baseline brain metastases, notably in patients who received prior treatment with crizotinib [35]. There has not been any reported significant neurologic toxicity associated with brigatinib [34].

27.2.5 Lorlatinib

In the setting of suspected ALK resistance, there may still be therapeutic benefit in use of additional ALK inhibitor therapy. Lorlatinib has activity against all known ALK inhibitor resistance mechanisms and was granted FDA approval for treatment of ALK-rearranged NSCLC following progression on crizotinib and an additional ALK inhibitor [35]. Although the optimal timing of lorlatinib in treatment of brain metastases remains under investigation, it has demonstrated activity within the CNS. Lorlatinib-related neurologic adverse effects reported included sensory peripheral neuropathy (30%), cognitive changes (18%), and dizziness (9%) of patients [35].

27.3 NTRK

The neurotrophin receptor kinase genes, NTRK1, NTRK2, or NTRK3, encode the TRKA, TRKB, and TRKC proteins (collectively known as the TRK family proteins) and have been under investigation for cancer therapy [36]. In cancer, TRK proteins can be activated by several mechanisms: somatic NTRK mutations (colorectal cancer, NSCLC, melanoma, and AML), activating splice variants of NTRK1 gene (neuroblastoma, AML), and through TRK overexpression (breast, cutaneous, and lung cancers) [37–42]. NTRK fusions have also been identified in rare cancers and are found at varying frequencies in adult and pediatric populations [43]. Among the NTRK TKIs, larotrectinib and entrectinib are in clinical development; entrectinib specifically has shown activity in brain metastases in preclinical and early-phase trials [44, 45].

27.3.1 Larotrectinib

Larotrectinib is a potent and selective inhibitor of all three TRK proteins, which has gained FDA approval for adult and pediatric patients with advanced solid tumors harboring an NTRK gene fusion. In a phase I study in adults and phase II study in pediatric patients with TRK fusion-positive cancers receiving larotrectinib, of 55 patients, dizziness (25%) and headache (2%) of all grades were reported to be related to treatment [43]. In the pooled analysis of 176 adult and pediatric patients, neurologic events of any grade occurred in 53% of patients including dizziness, gait disturbance, and paresthesias. There was one grade 4 encephalopathy occurring in one patient (0.6%) [43].

27.3.2 Entrectinib

Entrectinib is an oral, pan-TRK TKI which has additional activity against ROS1 and ALK [46]. To date, it has been tested in four clinical trials in patients harboring NTRK, ROS1, or ALK fusions [47]. In a combined safety analysis of two phase I trials of entrectinib in patients with advanced solid tumors, neurologic side effects included paresthesias (29%), myalgias (23%), and dizziness (19%) which were all grade 1 or 2; there was one grade 3 cognitive disturbance which improved with dose interruption [48].

27.4 Her2

Human epidermal growth factor receptor 2 (HER2), a member of the EGFR family of receptors, is an oncogene, also referred to as HER2/neu or ERBB-2. It is a predictive factor in breast cancer as its overexpression is associated with disease recurrence and overall worse prognosis [49]. There is a 12% 10-year risk of development of brain metastases in the setting of HER2-positive breast cancer. HER2 overexpression is found in 20% of breast cancers, and confirming status is essential in the care of patients with breast cancer as HER2 overexpressing tumors are likely to benefit from HER2-targeting agents. Furthermore, tumors which lack HER2 overexpression are less likely to benefit from such therapies [50]. In addition to clinical use in HER2-expressing breast cancers, the HER2-directed agents have also been used in management of HER2 overexpressing or amplified gastroesophageal adenocarcinoma [51].

27.4.1 Trastuzumab

Trastuzumab is a monoclonal antibody directed against HER2 and the only HER2-directed agent which has been associated with a survival benefit when combined with chemotherapy for adjuvant treatment of HER2-positive breast cancer [52]. There has been concern that while there is prolonged survival in Her2-positive breast cancer brain metastases with trastuzumab, this is owing to extracranial control of disease—as in the setting of an intact blood-brain barrier (BBB), the CNS penetration of trastuzumab is thought to be minimal [53, 54]. Additionally, following trastuzumab, the brain is frequently the first site of relapse in patients with HER2-positive disease. Headaches are among the most frequently reported treatment-related symptoms, noted in 10% of patients [52]. There have also been case reports of trastuzumab-induced migraine [55].

27.4.2 Ado-trastuzumab Emtansine

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate, composed of trastuzumab, a derivative of maytansine 1 (DM1), which is a microtubule inhibitor, and a thioether linker [56]. It is used as alternative first-line treatment for HER2-positive breast cancer or may also be used as second-line therapy with potential use in the setting of brain metastases. The phase III MARIANNE trial compared T-DM1 with placebo, T-DM1 and pertuzumab, trastuzumab, and taxane chemotherapy for advanced HER2-positive breast cancer. Peripheral sensory neuropathy was reported more frequently in the taxane with trastuzumab (20.1%) compared to the T-DM1 with pertuzumab (13%) and T-DM1 only arms (12%) [57]. The presence of microtubule inhibitor in T-DM1 has been proposed as a mechanism for development of neuropathy [58].

27.4.3 Lapatinib

Lapatinib is an EGFR1- and HER2-directed TKI which has been used in combination in various clinical scenarios for management of HER2-positive breast cancer and refractory brain metastases, specifically in combination with capecitabine. Neurotoxicity has not been observed with lapatinib [59].

27.4.4 Pertuzumab

Pertuzumab is a monoclonal antibody against HER2 which is combined with trastuzumab and taxane chemotherapy for treatment of previously untreated metastatic HER2-positive breast cancer. The role of pertuzumab in management of brain metastases remains under investigation. in the post hoc analysis of the phase III trial in which pertuzumab, trastuzumab, and taxane chemotherapy were compared with placebo, trastuzumab, and docetaxel, the median time to development of brain metastases was prolonged in comparison to the placebo group [60, 61]. In this phase III trial, across all grades, headaches (17%) and peripheral neuropathy (2.7%) were more frequent in the pertuzumab-treated group [60].

27.4.5 Neratinib

Neratinib is a dual-kinase inhibitor approved for adjuvant treatment following trastuzumab for early HER2-positive breast cancer [62]. It has not yet shown improvement in PFS or intracranial response rates in the setting of brain metastases [62]. In the randomized phase III trial ExteNET, the neurologic adverse effects reported including headaches (19%), muscle spasms (11%), and dizziness (10%) [63].

27.5 PARP Inhibitors

Poly (adenosine diphosphate [ADP]—ribose) polymerase (PARP) is essential to the repair of single-stranded DNA breaks through the base-excision repair (BER) pathway. Through synthetic lethality, PARP inhibition leads to formation of double-stranded DNA breaks which are unable to be accurately repaired in

tumors with homologous recombination deficiency [64, 65]. 15% of epithelial ovarian cancers are deficient in homologous recombination repair, likely owing to germline mutations in BRCA 1 and 2 [66, 67]. PARP inhibition is thus an attractive therapeutic option for treatment of ovarian cancer in women with BRCA 1 or 2 germline mutations as well as in breast cancer brain metastases, which demonstrate higher levels of homologous recombination deficiency [68].

27.5.1 Olaparib

Olaparib is a first-in-class oral PARP inhibitor which induces synthetic lethality in BRCA 1- and 2-deficient tumor cells. In a phase II study, olaparib monotherapy versus placebo, in patients with platinum-sensitive, relapsed high-grade serous ovarian carcinoma was associated with prolonged PFS and a lower rate of grade 3 and 4 toxicity [69]. In the olaparib-treated arm, the most common neurologic adverse effects were headache (18.4%) and asthenia (11.8%) [69]. In a separate phase I study, olaparib was combined with paclitaxel and/or carboplatin and then subsequently continued on olaparib monotherapy [70]. Three of 21 patients stopped combination therapy due to development of peripheral neuropathy [70].

27.5.2 Veliparib

In the phase II trial I-SPY 2, veliparib, an oral PARP-1 and PARP-2 inhibitor, showed improved pathological complete responses in patients with early breast cancer treated with veliparib in combination with neoadjuvant chemotherapy [71]. A subsequent phase III study, BrighTNess, showed that while there was an increase in the pathological complete response with the addition of veliparib and carboplatin to paclitaxel followed by cyclophosphamide and doxorubicin, the addition of veliparib to carboplatin and paclitaxel did not [71]. In the veliparib-treated group, peripheral sensory neuropathy (38%), dysgeusia (19%), and dizziness (14%) were more frequent than in the veliparib placebo groups [71].

27.6 Cyclin-Dependent Kinase (CDK) Inhibition

The cyclin-dependent kinases (CDK), specifically CDK 4/6 in combination with cyclin D, are critical drivers of cell proliferation and thus provide a therapeutic opportunity for cancer treatments due to disordered cell cycle regulation [72, 73]. Development of inhibitors of CDK 4/6 has been an exciting area of exploration of potential cancer therapies, specifically in treatment of breast cancer brain metastases.

27.6.1 Palbociclib

Palbociclib is an oral CDK inhibitor currently FDA approved for metastatic, hormone receptor (HR)-positive, HER2-negative metastatic breast cancer, in combination with the aromatase inhibitor (AI) letrozole [74]. In a phase III study, patients with untreated, HER-negative, HR-positive breast cancer were randomized to either palbociclib and letrozole or placebo and letrozole. No neurologic adverse effects were reported [74]. In an earlier phase II study, the most common neurologic adverse effects were headaches (14%), dizziness, and peripheral neuropathy (10%) [75].

27.6.2 Abemaciclib

Abemaciclib is an oral CDK inhibitor FDA approved for initial treatment of postmenopausal women with HR-positive, HER2-negative breast cancer, as shown in the phase III study MONARCH 3 [73]. Only headaches (15.6%) were reported in the abemaciclib treatment arm [73]. Abemaciclib has also been used in management of HR-positive, HER2-negative breast cancer brain metastases and metastatic KRAS-mutated NSCLC [73, 76].

27.6.3 Ribociclib

Ribociclib is approved in combination with letrozole in postmenopausal women with metastatic or advanced HER2-negative, HR-positive breast cancer [77]. In a comparison of letrozole monotherapy and ribociclib plus, headaches occurred in 26.9% of patients who received ribociclib [77]. This combination is currently under investigation in a phase I trial in treatment of breast cancer brain metastases (NCT03096847).

27.7 Phosphoinositide-3-Kinase (PI3K) Inhibitors

Phosphoinositide-3-kinase (PI3K) pathway is a signal transduction pathway and one of the most active cell signaling pathways in human cancer [78]. PI3K isoforms (gamma and delta) are major effectors of receptor tyrosine kinases, transducing signal into intracellular messages [78]. PI3K delta is constitutively active in hematologic malignancies, and its inhibition targets proliferation and survival of leukemia and lymphoma cells. PI3K gamma reduces differentiation and migration of cells within the tumor microenvironment, which support and protect malignant cells [79]. For these reasons, the PI3K pathway is a rationale target for therapeutic interventions in treatment of hematologic malignancies and in combination with hormonal therapy for breast cancer brain metastases [80].

27.7.1 Idelalisib

Idelalisib is an oral, selective PI3K delta inhibitor which promotes apoptosis, approved currently for treatment of recurrent chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) in combination with rituximab. Early-phase clinical trials established antitumor activity as well as safety in CLL patients and in the context of indolent non-Hodgkin's lymphoma (NHL) [81]. A large, phase III randomized trial of idelalisib and rituximab versus placebo and rituximab in relapsed/refractory CLL demonstrated improved ORR on the idelalisib arm as well as prolonged OS [82]. In this trial, no significant neurologic adverse effects were reported.

27.7.2 Duvelisib

Duvelisib is a dual inhibitor of PI3K delta and gamma, which has shown antitumor activity also in management of relapsed/refractory CLL/SLL. It gained recent FDA approval as monotherapy for relapsed/refractory CLL/SLL following failure of two prior lines of therapy. In two phase I trials, duvelisib was associated with significant clinical responses across multiple disease types including indolent NHL, relapsed/refractory CLL, and peripheral and cutaneous T-cell lymphoma (TCL) [82, 83]. Headache was reported in 18% of patients who received duvelisib [83].

27.8 Bruton's Tyrosine Kinase (BTK) Inhibitors

Bruton's tyrosine kinase (BTK) is a Tec kinase which is critical to B-cell receptor (BCR) signaling, which is activated in CLL. When activated, BTK leads to downstream activation of cell survival pathways including MAPK and NF-kappa B [84]. BTK inhibition is a promising therapeutic target for treatment of hematologic malignancies, with investigations underway for its role in CNS relapse of disease [84, 85].

27.8.1 Ibrutinib

Ibrutinib is a first-in-class, oral, selective BTK inhibitor which is FDA approved for untreated and previously treated CLL. Its use has also been explored in CNS relapse of mantle cell lymphoma, which occurs in 4.1% of cases [85]. Ibrutinib binds to its target (cysteine-481 residue of BTK) and thus interrupts BCR signaling leading to B-cell apoptosis [84]. The most devastating complication associated with ibrutinib is hemorrhage from any site; however, there have been few cases of reported intracranial hemor-

rhage [86]. Other neurologic adverse effects noted include headache, which was reported in 13.8% of patients receiving ibrutinib [87].

Ibrutinib can cause hypogammaglobulinemia, thus predisposing patients with CLL to infections, namely, of the upper respiratory tract and other bacterial and fungal infections which occur in the setting of immunosuppression, specifically pneumocystis carinii and aspergillus [88–90]. Progressive multifocal leukoencephalopathy (PML) is a rare but devastating neurologic disease which is triggered by the polyoma John Cunningham (JC) virus, which has been reported in a patient with CLL following treatment with ibrutinib [91].

27.8.2 Acalabrutinib

Acalabrutinib is an irreversible BTK inhibitor which has properties designed to be more selective and specific in comparison to ibrutinib, with less off-target effects [92]. Phase I/II studies in patients with relapsed CLL have shown ORR which have been consistent across all high-risk subgroups with 95% of patients showing some response to therapy [92]. The most common adverse effect was headache in 43% of patients [92]. As with ibrutinib, cases of PML have also occurred during treatment with acalabrutinib [93].

27.9 BRAF and MEK Inhibitors

BRAF is a serine threonine kinase and a member of the RAF kinase family, as part of the RAF/MEK/ERK serine threonine kinase cascade which regulates cell growth and differentiation and has been associated with human cancers [93]. Activating mutations in BRAF are present in up to 60% of advanced melanoma, with 80–90% of the mutations consisting of the substitution of glutamic acid for valine at position 600 (V600E); the remaining mutations involve substitution of glutamic acid for lysine (V600K) [93]. A phase I study with an oral BRAF inhibitor in patients with BRAF-mutated metastatic melanoma showed complete or partial tumor regression in 11 of 16 patients in the dose-escalation cohort and in 26 of 32 patients in the extension cohort [94]. BRAF inhibitors have demonstrated impact as monotherapy, but now combination regimen with MEK inhibitors has supplanted monotherapy. MEK or MAPK kinase is downstream of BRAF and has been associated with improved PFS and OS in BRAF-mutated melanoma [95–97]. These agents have established activity in the CNS, with combination BRAF/MEK inhibition being preferred therapy in certain settings. In addition to the combination regimens discussed here, investigation of encorafenib and binimetinib is ongoing [98].

27.9.1 Dabrafenib and Trametinib

Dabrafenib is an oral reversible BRAF inhibitor which has demonstrated activity in treatment of advanced melanoma, both as monotherapy and in combination with MEK inhibition. In a phase III trial, comparing dabrafenib to dacarbazine in patients with unresectable stage III or IV melanoma harboring BRAF mutations, headaches were reported in 5% of patients receiving dabrafenib [95].

Dabrafenib has been combined with MEK inhibition (trametinib) to delay development of resistance and to mitigate non-neurologic toxicity of BRAF inhibition. Trametinib is a highly selective inhibitor of MEK1/MEK2 and was initially approved as monotherapy for BRAF-mutated melanoma. In evaluation of combination therapy, two phase III trials of dabrafenib/trametinib have been conducted: in one, the combination of dabrafenib and trametinib was compared to dabrafenib and placebo. Neurologic adverse effects were uncommon with combination treatment. Ocular symptoms have been reported with trametinib but are also quite rare [99].

27.10 Bcr-Abl

The driver event in chronic myelogenous leukemia (CML) is the translocation between the long arms of chromosomes 9 and 22, resulting in a shortened chromosome 22 also known as the Philadelphia chromosome (Ph) [100]. The manifestation of which is the formation of the fusion gene *BCR-ABL1* on chromosome 22, which is found in over 90% of CML patients [100, 101]. There are three common variants of the BCR-ABL1 proteins which result from the translocation, which is determined by the site of the break point. Oral TKIs are the standard of care in treatment of CML for initial management. A newer second-generation TKI, radotinib, has gained approval outside of the US for initial treatment of CML or TKI-refractory CML [102]. Arterial ischemic events have been described as a class-wide effect of TKIs, including cerebrovascular involvement [103]. To date, these drugs have not been studied in brain metastases or are reported to have minimal activity in the CNS [104].

27.10.1 Imatinib

Imatinib is a first-generation TKI and the first TKI available for use in patients with CML in chronic phase (CP CML) [105]. Prospective trials have compared imatinib to interferon in combination with cytarabine in initial treatment for CP CML [105]. In the imatinib-treated group, headache was the most common neurologic adverse effect, reported in 31.2% of patients [105].

27.10.2 Dasatinib

Dasatinib is a second-generation BCR-ABL TKI which gained initial approval for second-line treatment of CML in the setting of imatinib failure [106]. The DASISION trial was a randomized phase III study in which dasatinib was compared to imatinib in treatment-naive CML [107]. Among ten cardiovascular ischemic events which occurred within 1 year of dasatinib, there were two transient ischemic attacks [107]. Also noted was one death secondary to Klebsiella meningoencephalitis [107].

27.10.3 Bosutinib

Bosutinib is an oral TKI and inhibitor of ABL and SRC kinase FDA approved also for initial treatment of CP CML. In a phase II study of bosutinib in recurrent glioblastoma, in which nine patients were enrolled, seizure and cerebral edema were reported; however, these were not attributed to bosutinib [108].

27.10.4 Ponatinib

Ponatinib is approved in the US for adult patients with refractory CML or Philadelphia-positive (Ph+) acute lymphocytic leukemia (ALL), as well in those with BCR-ABL threonine to isoleucine (T315I) mutation [109]. In a phase II trial of ponatinib in patients with CML or Ph+ ALL, headaches were reported in 23% of patients with chronic-phase CML [109]. As with other TKIs, peripheral neuropathies are uncommon but may occur [110]. Ponatinib has been associated with peripheral arterial occlusive disease. As such, there may also be risk of cerebrovascular disease given this toxicity profile. Case reports of ocular arterial thrombosis have been reported with ponatinib [111].

27.11 JAK Inhibitors

27.11.1 Ruxolitinib

Ruxolitinib is an FDA-approved, selective Janus kinase 1 and 2 (JAK) inhibitor used for treatment of myelofibrosis [112]. In 2005, the JAK2 V617F mutation was identified and is the most common molecular abnormality in myeloproliferative neoplasms [113, 114]. JAK2 mutations are pres-

ent in 50% of patients with primary myelofibrosis [115]. There were no neurologic adverse effects noted in a trial of ruxolitinib [112]. Other JAK inhibitors have yet to be approved due to significant off-target effects including with neurologic toxicity [116].

27.12 Antibody-Drug Conjugate

27.12.1 Brentuximab

Brentuximab vedotin is an anti-CD30 antibody-drug conjugate approved for relapsed and refractory Hodgkin's lymphoma. In a randomized, phase III trial, brentuximab, doxorubicin, vinblastine, and dacarbazine (A+AVD) was compared to doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Peripheral neuropathy occurred in 67% of patients in the A+AVD group with trial drug being discontinued in 10% of patients [117]. Peripheral neuropathy by brentuximab is caused by disruption of axonal transported and is predominantly sensory with 11% of patients experiencing motor symptoms [118].

27.13 Radiolabeled Antibodies

27.13.1 Ibritumomab

Radioimmunotherapy links monoclonal antibodies to radiolabeled isotopes. 90Y-Ibritumomab tiuxetan is an anti-CD20, murine monoclonal antibody, combined with a chelator tiuxetan that is conjugated to the radioisotope yttrium-90, subsequently combined with radiation as treatment for patients with relapsed or treatment-refractory follicular lymphoma. Its use has been limited by severe toxicity, specifically cytopenias and reports of treatment-related myelodysplastic syndrome and acute myeloid leukemia [119]. In a randomized trial of ibritumomab, headaches were most frequently reported in patients receiving ibritumomab; however, all were grade 1 and 2 adverse effects [120].

27.14 SMO

The smoothened (SMO) receptor is one of the main upstream transducers of the sonic hedgehog (SHH) signaling pathway, which is activated aberrantly in disease and thought to be an essential component of tumorigenesis [121]. SMO is a validated target for use in anticancer therapy with FDA approval for SMO antagonists vismodegib and sonidegib, both approved for advanced basal cell carcinomas with investigations underway for other indications including SHH-dependent medulloblastoma and progressive meningioma (NCT02523014) [121, 122]. SMO mutations have been identified infrequently in NSCLC brain metastases [123, 124].

27.14.1 Vismodegib

Vismodegib is a first-in-class SMO inhibitor FDA approved for treatment of adults with metastatic or locally advanced basal cell carcinoma which is not appropriate for surgery or radiation. In the STEVIE trial, safety of vismodegib was assessed in patients with advanced or metastatic basal cell carcinoma [125]. Muscle spasms were the most frequently reported treatment-emergent adverse effect reports, occurring in 98% of patients; headaches were reported in 10.8% of patients [125]. When also studied in the pediatric population, vismodegib is also not associated with any significant neurotoxicity [126].

27.14.2 Sonidegib

Sonidegib is a selective inhibitor of SMO which has demonstrated high tissue penetration (including blood-brain barrier) and oral bioavailability. In a phase I study of sonidegib in adult patients with advanced solid tumors, similar to vismodegib, muscle spasms were the most frequently reported in 32% of patients [127].

27.15 HDAC Inhibitors

Histone deacetylases (HDAC) are involved in chromatin remodeling and epigenetic regulation of gene expression, which is important in cancer growth. Altered histone deacetylation has been found in several solid tumors and is the target of HDAC inhibitors. The addition of HDAC inhibitors to radiation has been investigated in the treatment of breast cancer brain metastases [128].

27.15.1 Vorinostat

Vorinostat is an orally active, potent inhibitor of HDAC, which functions by binding to a zinc ion in the catalytic domain of the enzyme [129]. It is FDA approved for treatment of cutaneous manifestations of cutaneous T-cell lymphoma, with investigations ongoing for other solid tumors [130, 131]. In a prior trial of patients with AML, there was one case of grade 4 intracranial hemorrhage and grade dizziness [132]. No other neurotoxicity has been reported.

27.15.2 Panobinostat

Panobinostat is a pan-HDAC inhibitor which has potent inhibitory activity at low concentrations against all classes of HDAC enzymes [133]. It is FDA approved in combination with bortezomib and dexamethasone for patients with multiple myeloma (MM), who failed at last two previously lines of therapy. In a large phase III study of panobinostat, bortezomib, and dexamethasone, peripheral neuropathy was the most common neurologic adverse effect noted in the panobinostat cohort at 61% with 17% of patients experiencing grade 3 or 4 peripheral neuropathy [134]. Sixty-seven percent of patients randomized to placebo reported peripheral neuropathy, although with fewer grade 3 or 4 toxicity [134].

27.15.3 Belinostat

Belinostat is a pan-HDAC inhibitor which has been studied in patients with solid and hematologic malignancies, now currently FDA approved for relapsed or refractory T-cell lymphoma [135]. It carries both antitumor and antiangiogenic properties [135]. In a phase II study assessing the safety and efficacy of belinostat in patients with relapsed or recurrent primary TCL or cutaneous TCL, dizziness and headaches were reported in 5 and 1 patient, respectively, among treatment-emergent adverse effects [135].

27.15.4 Valproic Acid

Valproic acid (VPA) is a class I HDAC inhibitor whose best-known indication has been for treatment of seizure disorders but has gained attention for its potential role as a cancer therapy [136]. In a small phase I study of eight patients with metastatic neuroendocrine carcinoma on VPA monotherapy, partial response was noted in one patient with five patients achieving stable disease. VPA was also studied in combination with 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide in 15 patients with metastatic breast cancer, producing objective responses in 64% of patients [137]. In a trial of eight patients with advanced NSCLC, neurotoxicity was dose-limiting as somnolence, ataxia, and memory loss were observed [138].

27.16 Proteasome Inhibitor

Proteasomes are present in all cells and carry the responsibility of degrading proteins which regulate cell cycle progression, specifically an endogenous inhibitor of NF-kappa B, I kappa B. The result of degradation of I kappa B is activation of NF-kappa B, which upregulates proteins which promote cell survival, thus reducing likelihood of apoptosis [139]. This activation of NF-kappa

B has been implicated in the growth, survival, and migration of myeloma cells [139]. As such proteasome inhibitors form the backbone for treatment of multiple myeloma. Peripheral neuropathy is commonly reported with proteasome inhibitor therapy.

27.16.1 Bortezomib

Bortezomib is a first-in-class proteasome inhibitor approved for treatment of multiple myeloma and mantle cell lymphoma. Peripheral nerve injury is the most frequent and significant non-hematologic toxicity associated with bortezomib given impact of quality of life and impact upon treatment regimen [140]. Peripheral neuropathy was assessed in two phase II studies of 256 patients with relapsed/refractory multiple myeloma. Prior to start of therapy, 81% of evaluable patients were found on exam to have baseline peripheral neuropathy. Treatment-emergent neuropathy was reported in 35% of patients receiving higher doses of bortezomib (1.3 mg/m^2) versus 21% receiving 1 mg/m^2 [140]. Grade 3 and higher toxicity were more frequent in patients with baseline peripheral neuropathy. Bortezomib typically causes a painful, sensory neuropathy thought to be secondary to direct toxicity on the dorsal root ganglion [141]. Other patterns including motor and autonomic neuropathy have been reported [141, 142]. Guidelines for management for bortezomib-induced peripheral neuropathy have also been established by the International Myeloma Working Group [143]. Bortezomib has been linked to central nervous toxicity including PRES and cerebellar toxicity [144–146].

27.16.2 Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor approved for treatment of progressive multiple myeloma in patients previously treated with bortezomib and immunomodulatory therapy as well as in combination with dexamethasone and lenalidomide for heavily pretreated multiple myeloma. In comparison to bortezomib, carfilzomib causes a milder peripheral neuropathy, likely the result of less off-target effects [147]. Combined safety data from four phase II trials of single-agent carfilzomib was evaluated. Of 526 evaluable patients, 378 patients (71.8%) had active peripheral neuropathy at the time of trial enrollment [147]. During the course of trial, only 13.9% of patients reported peripheral neuropathy with only 1.3% being grade 3 or higher [147].

27.16.3 Ixazomib

Ixazomib is an oral proteasome inhibitor currently under investigation for treatment of multiple myeloma. In a phase III study of ixazomib, peripheral neuropathy of any grade was reported in 27% of patients versus 22% in the placebo group [153]. Similar to carfilzomib, ixazomib is associated with less severe peripheral neuropathy when compared to bortezomib.

27.17 mTOR Inhibitors

The mammalian target of rapamycin (mTOR) signaling pathway is a central regulator cell metabolism, growth, proliferation, and survival [148]. The mTOR pathway plays a critical role in normal and disease states, specifically tumor formation and angiogenesis, and as such is the target of inhibition by several antitumor therapeutic agents [150]. mTOR inhibitors function by binding to the FK-binding protein and modulate mTOR. In addition to its use as antirejection therapy in the setting of renal transplantation, mTOR inhibitors have gained approval for use in tuberous sclerosis and renal cell carcinoma and have been investigated in combination with PI3K inhibitors in breast cancer brain metastases [151, 152]. Calcineurin inhibitors, which include mTOR inhibitors, as a class, have been associated with neurotoxicity [153].

27.17.1 Everolimus

Everolimus is an mTOR inhibitor which has been used in combination therapy with aromatase inhibitor (AI) in postmenopausal women with AI-resistant, advanced ER-positive breast cancer. As activating mutations in mTOR pathway are common in breast cancer, this makes for a logical therapeutic option in managing disease [154]. In a phase III study comparing everolimus and exemestane to exemestane and placebo, headaches were reported in 19 patients in the everolimus treatment arm in comparison to 13 in the placebo arm [155].

27.17.2 Sirolimus

Similar to everolimus, sirolimus acts by blocking the response of T- and B-cell activation by cytokines, thus preventing cell cycle progression and proliferation [156]. Sirolimus has been increasingly used for treatment of angiomyolipomas in tuberous sclerosis and has shown some antimalignancy effects in the setting of posttransplant squamous cell carcinoma [157, 158]. Sirolimus has not been associated with significant neurotoxicity except when used in combination with cyclosporine A [159].

27.17.3 Temsirolimus

Temsirolimus is a highly specific inhibitor of mTOR which acts by binding the intracellular protein FKBP-12, forming an inhibitory complex of mTOR, causing cell cycle arrest and tumor suppression [160]. Along with everolimus, temsirolimus is approved for advanced renal cell carcinoma and has been used off-label for locally advanced, recurrent or metastatic endometrial cancers. In a report of temsirolimus-related adverse effects from the phase III Global Advanced Renal Cell Carcinoma (ARCC) trial, there were no grade 3 or 4 neurologic side effects [160]. In a study of 35 patients with mantle cell lymphoma receiving weekly temsirolimus 250 mg, there was one case each of grade 3 muscle weakness, motor neuropathy, cranial neuropathy, blurred vision, and headache, with one case of grade 4 decrease consciousness [161].

27.17.4 VEGF

The vascular endothelial growth factor (VEGF) family was first identified and isolated in 1989 with its main effector, the VEGF ligand, known to be a key mediator of angiogenesis in cancer [162–164]. VEGF acts by binding to either of its receptors, VEGF receptor 1 or 2 (VEGFR-1/VEGFR-2), which, under physiologic states, promotes angiogenesis for essential functions such as embryonic development and wound healing [164]. In cancer, VEGF is upregulated, allowing for tumor cell growth to occur by formation of new tumor vasculature. Several antitumor agents have been developed to target either VEGF or its receptors [164].

As a class, nearly all of the VEGF and VEGF receptor inhibitors have been implicated in the development of hypertension as well as increased risk of arterial thromboembolic events [165, 166]. The mechanism for increased risk of thromboembolism remains under investigation; however, it is thought to be related to disruption of tumor-associated endothelial cells, "switching" the endothelium from an anticoagulant to a prothrombotic state [167]. Reversible posterior leukoencephalopathy (RPLS) has also been reported as a class-wide phenomenon in the setting of VEGF inhibition and is thought to be secondary to disordered cerebral autoregulation and capillary dysfunction [168].

27.17.5 Cabozantinib

Cabozantinib is a small-molecule TKI currently used for treatment of advanced renal cell carcinoma (mRCC) and progressive, metastatic thyroid cancer. In addition to its effects on the

VEGF receptor, as well as on the MET and AXL genes, both of which portend poor prognosis when present as they may predict resistance to VEGF receptor inhibition [169]. In a randomized phase II comparing cabozantinib to sunitinib as first-line therapy for mRCC, dysgeusia was the most common neurologic toxicity: noted in 41% of patients receiving cabozantinib [169]. In METEOR, a phase III trial of patients with advanced clear cell RCC who had been previously treated with VEGFR therapy, patients were randomized to either cabozantinib or everolimus. In patients receiving cabozantinib, 7.3% of patients had venous thromboembolic events and 0.9% had arterial events [170]. A rare but serious complication of cabozantinib is RPLS, though this was not observed in METEOR.

27.17.6 Lenvatinib

Lenvatinib is an oral multitargeted TKI with activity against VEGF receptors 1–3, FGFR, PDGFR-alpha, RET, and KIT proto-oncogenes, currently used for radioiodine-refractory differentiated thyroid cancer and for combination therapy with everolimus for advanced RCC following prior anti-VEGF treatment [171]. There have been case reports of lenvatinib-associated PRES [172, 173].

27.17.7 Sorafenib

Sorafenib is an oral multitargeted TKI which acts on several factors including VEGF receptor 2, FLT3, PDGF receptor, FGFR1, C-raf, and B-raf. It is used for treatment of previously untreated and previously treated advanced RCC. In a phase II trial, patients with metastatic clear cell RCC were randomized to either bevacizumab monotherapy, bevacizumab and temsirolimus, bevacizumab and sorafenib, or sorafenib and temsirolimus [174]. Grade 3 headaches were noted in all treatment groups [174]. In a phase II of first-line sorafenib versus interferon alfa 2a, confusion was the only adverse effect attributed to sorafenib, reported in 1 patient. A phase III study of sorafenib in advanced RCC, sensory neuropathy was reported in 13% of patients receiving sorafenib [175]. Brain metastases secondary to mRCC have propensity to hemorrhage; however, in a review of the incidence of CNS bleeding, anti-VEGF TKIs, including sorafenib and sunitinib, and anti-VEGF monoclonal antibody, bevacizumab, were not associated with increased risk of CNS hemorrhage [176].

27.17.8 Sunitinib

Sunitinib is a VEGF receptor TKI with effects also on PDGF receptor and the c-kit oncogene. In a phase III comparing sunitinib to interferon alfa in mRCC, headaches were reported in 11 of 375 patients in the sunitinib arm in comparison to 14 of 360 treated with interferon [177]. Sunitinib-associated AIDP and cognitive impairment have also been reported [178, 179].

27.17.9 Pazopanib

Pazopanib is an oral TKI which acts on VEGF, PDGR, and kit receptors and used for locally advanced or mRCC. In a phase III trial of pazopanib, headaches were reported in 30% of patients [180]. Other trials have shown pazopanib to be reasonably tolerated with side effect profile similar to other VEGF/VEGFR inhibitors [181]. Myalgias and muscle spasms have been described in association with pazopanib [182].

27.17.10 Axitinib

Axitinib is an oral TKI with activity against VEGF receptors 1, 2, and 3 currently used for advanced renal cell carcinoma. In a phase II study of axitinib in refractory mRCC, headaches were reported in 29% of patients treated with axitinib [183]. Two patients treated with axitinib were found to have cerebral hemorrhage, one of whom had an underlying brain metastasis [183]. In a phase II study with and without dose titration of axitinib in mRCC, headaches and dizziness were

reported at higher frequency in the axitinib titration arms [184]. No other specific neurotoxicity has been reported with axitinib.

27.17.11 Regorafenib

Regorafenib is an oral small-molecule multikinase inhibitor which is active against VEGF receptors, stromal and oncogenic receptor tyrosine kinases, currently FDA approved for treatment of heavily pretreated metastatic colorectal cancer (mCRC) [185]. In a phase III trial of regorafenib monotherapy in mCRC, sensory neuropathy (7%) and headaches (5%) were reported in the regorafenib-treated arm [185]. There have been isolated case reports of hyperammonemic encephalopathy and transverse myelitis in patients on regorafenib [186].

27.17.12 Vandetanib

Vandetanib is an oral inhibitor of VEGFR, RET, and EGFR used for treatment of patients with metastatic or unresectable hereditary MTC or multiple endocrine neoplasia type 2a [187]. In a phase II of vandetanib, headaches (47%) and dysgeusia (33%) were among the neurologic adverse effects noted [187]. In a phase I/II trial of vandetanib in 64 patients with recurrent malignant glioma, among the ≥ grade 3 adverse effects included seizure (ten patients) and intracranial hemorrhage (one patient) [188]. There were also two other patients who experienced symptomatic intracranial hemorrhage [188].

27.17.13 Bevacizumab

Bevacizumab is a monoclonal antibody against VEGF, which inhibits binding of the VEGF ligand to its receptor. It has been used widely for treatment of multiple diseases, gaining FDA approval for macular degeneration, metastatic CRC, metastatic NSCLC, RCC, ovarian cancer, cervical cancer, and recurrent/progressive glioblastoma. In the phase III AVAGLIO trial in which bevacizumab was added to standard therapy of temozolomide and radiotherapy for newly diagnosed glioblastoma, patients were randomized to either bevacizumab or placebo [189]. In the bevacizumab-treated arm, cerebral hemorrhage of all grades was reported in 3.3% of patients, with 2% of hemorrhages being grade 3 or higher, more frequent than in the placebo group [189]. There has been ongoing debate around whether bevacizumab, in the setting of known intracranial metastases, increases risk of hemorrhage. In an evidence-based review of the incidence of hemorrhage in NSCLC-associated metastases, bevacizumab was not associated with an increased risk of bleed [176]. Similarly, in a phase II of bevacizumab in recurrent glioblastoma, patients received bevacizumab monotherapy followed by irinotecan and bevacizumab combination therapy, and there were no intracranial hemorrhage among the adverse effects [190]. Consistent with the larger class of antiangiogenic TKIs, bevacizumab has also been implicated in the development of RPLS and associated conditions [191, 192].

27.17.14 Ramucirumab

Ramucirumab is a recombinant monoclonal antibody of immunoglobulin G1 (IgG1) class which binds and blocks activation of VEGFR-2. It is currently used for advanced gastric cancer, NSCLC, and mCRC. In a meta-analysis of safety data from six completed phase III trials of ramucirumab, of six bleeding events reported during treatment of ramucirumab, two were intracranial hemorrhage [193]. There were seven grade 5 arterial thromboembolic events (ATE), including one cerebrovascular on ramucirumab, in comparison to 10 total ATEs on the control arm and three cerebrovascular events [193].

27.17.15 Ziv-aflibercept

Aflibercept is an inhibitor of the VEGF ligand by blocking its binding to all class of VEGFRs, and placenta growth factor (PIGF) binds to

VEGFR-1. It is approved for use in combination with chemotherapy for mCRC. In a phase I study of aflibercept administered subcutaneously to patients with advanced solid tumors, cerebral ischemia of any grade was reported in 3% of all patients [194]. A retrospective review of pooled safety data of 1562 patients who received intravitreal aflibercept, among intraocular adverse effects, central retinal artery occlusion (CRAO) was found in two patients [194]. There was one patient with stroke which was nonfatal [195].

27.18 Summary

Novel cancer therapies have been adopted into treatment regimens and, in some diseases, represent the new standard of care. As these therapies have resulted in improvement in response rates and survival, newer toxicities have emerged involving the central and peripheral nervous systems. Although the majority of neurological adverse effects are rare, they may be severe, and with increasing familiarity of the tumor-directed qualities of these drugs, recognition of patterns will be important in order to avoid loss of neurologic function. Furthermore, increasing knowledge of treatment-related neurologic toxicities will hopefully reduce misdiagnosis and the time to intervention.

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