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An overview of current results with the vincristine-irinotecan-temozolomide combination with or without bevacizumab in pediatric, adolescence and adult solid tumors

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ABSTRACT

Malignant tumors in young patients present a significant therapeutic challenge for physicians, partially due to their rarity and a relative lack of data, at least compared to adult tumors. As a result, there is an urgent need to explore new possible therapeutic regimens, either by introducing novel agents or by exploring combinations of existing agents. Vincristine, Temozolomide and Irinotecan are chemotherapeutic drugs which have emerged over the last six decades as monotherapy or as part of therapeutic regimens in various solid tumors. Combining these agents can yield strong synergistic effects, as suggested by preclinical data and results from clinical trials. Furthermore, adding novel molecules, such as anti-VEGF factor Bevacizumab to the aforementioned regimens, has shown efficacy in a limited number of trials, which are thoroughly analyzed throughout this review. Data presented throughout this paper suggest that VIT(b) regimen should be further explored in solid tumors in pediatric and adolescent patients.

1. Introduction

The combination of vincristine - irinotecan - temozolomide (VIT) with or without the addition of bevacizumab (VITb) has been an effective regimen in the treatment of rhabdomyosarcoma and has produced encouraging results in various solid tumors of children, adolescent and young patients. The purpose of this review is to review the main applications of VIT and VITb regimens in oncology to date, as well as to suggest their potential in other types of cancer, that may be worth studying in the context of well-designed clinical trials.

2. Methods

2.1. Studies selection

A bibliographic survey using the terms "vincristine" AND "irinotecan" AND "temozolomide" AND "bevacizumab" was conducted in PubMed/Medline database. Search included reviews, systematic reviews, clinical trials, case series and case reports; abstracts referring to the same regimens from ESMO and ASCO congresses within the last 5 years were also reviewed.

2.2. Definition of responses

The studies chosen in this review evaluated effectiveness of VIT with or without bevacizumab in adolescent and pediatric patients with solid tumors. Primary endpoints in most studies were overall response rate (ORR), according to RECIST 1.1 criteria (Schwartz et al., 2016) or progression free survival (PFS) measured in median time to progression or as a percentage of patients without disease progression within 1 or 2 years' period. Patients' response was usually evaluated with imaging after the first 2 or 3 cycles of chemotherapy. Overall survival (OS) and disease control rate (DCR) were also evaluated in some studies as secondary endpoints. OS was also measured either as median time from baseline to death from any cause, or as a percentage of patients alive within a 1 or 2 years' period.

3. Chemotherapy drugs and mechanism of action

3.1. Temozolomide

Temozolomide is a non-classic alkylating agent with antitumor activity related to methylation of DNA, mainly of guanine particles.

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Metabolic activation to the reactive compound 3-methyl-(triazen-1-yl)-imidazole-4-carboxamide (MTIC) is required to exert its antitumor effect (Newlands et al., 1997). Its cytotoxicity is dependent upon DNA repair activities and protracted temozolomide regimens lead to depletion of the DNA-repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) (Tolcher et al., 2003). It has been approved in the treatment of adults with newly diagnosed glioblastoma multiforme (GBM) undergoing concomitant radiotherapy and later as maintenance treatment, as well as for the treatment of refractory anaplastic astrocytoma with disease progression on the commonly applied nitrosourea and procarbazine containing regimens. Most common adverse reactions include alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia and convulsions. Hematologic toxicity is also common (FDA, 2021a).

3.2. Irinotecan

Irinotecan, a camptothecin prodrug, converts to SN-38, a potent topoisomerase-I poison, by endogenous carboxylesterases leading eventually to enzyme-DNA covalent complex stabilization and S-phase specific cytotoxicity. It is more efficient when used at a protracted low dose for five consecutive days for 2 weeks in a row (Wagner, 2011). It is FDA approved for metastatic colorectal cancer as first-line therapy in combination with 5-fluorouracil and leucovorin and for recurrent or progressive disease following initial 5-fluorouracil-based therapy. Contraindications include chronic inflammatory bowel disease and/or intestinal obstruction, severe bone marrow failure, WHO performance status > 2 and total bilirubin > 3 times the upper limit normal. Common adverse reactions include nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia, anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin and alopecia (FDA, 2021b). Irinotecan has demonstrated encouraging antitumor efficacy against brain tumors and rhabdomyosarcoma (RMS) in preclinical studies (Houghton et al., 1995). An anti-angiogenic effect may also be achieved via 5-day courses of irinotecan through inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) (Guerin et al., 2012).

3.3. Vincristine

Vincristine sulfate is considered to inhibit microtubule formation in mitotic spindle, thus leading to an arrest of the divided cells at the metaphase stage (Islam and Iskander, 2004). It is FDA approved for acute lymphoblastic leukemia, while it is also useful in combination with other agents in Hodgkin's disease, malignant lymphomas, RMS, neuroblastoma and Wilms' tumor. Vincristine is also part of standard of care chemotherapy regimens for Ewing's Sarcoma (ES) in combination with other agents. It is contraindicated in patients with the demyelinating form of Charcot-Marie-Tooth syndrome and the main adverse events include alopecia, leukopenia, neuropathic pain, constipation, sensory loss, paresthesia, walking difficulty, slapping gait, loss of deep-tendon reflexes and muscle wasting (FDA, 2021c).

3.4. Bevacizumab

Bevacizumab is a vascular endothelial growth factor (VEGF)-specific angiogenesis inhibitor that prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. It is approved for metastatic colorectal cancer with intravenous 5-fluorouracil-based regimens for first- and second-line treatment, for non-squamous non-small cell lung cancer with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease, and for HER-2 negative metastatic breast cancer with paclitaxel for patients who have not received chemotherapy. Bevacizumab has received FDA approval in the treatment of patients withGBM as a single agent for patients with progressive disease following prior therapy, based on two phase II and one phase III studies that showed an increase in progression free survival, but not in overall survival. Thus, EMA has not approved its use in GBM. Most common adverse events include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, delayed wound healing, lacrimation disorder and exfoliative dermatitis (FDA, 2021d).

4. Rationale for Combined Treatment

4.1. Temozolomide – irinotecan

Irinotecan and temozolomide have shown synergistic antitumoral activity occurring when temozolomide is administered prior to irinotecan. This could be attributed to the placement of an adduct at the O6 position of guanine, leading to recruitment of topoisomerase-1 DNA covalent complexes and eventually increasing the cytotoxicity of irinotecan (Houghton et al., 1995; Pourquier et al., 2001). This combination has shown enhanced activity in a variety of solid tumors including recurrent malignant gliomas (Gruber and Buster, 2004; Reynes et al., 2014), ES (Casey et al., 2009; Wagner et al., 2007; McCabe et al., 2020) and neuroblastoma (Wagner et al., 2009; Kushner et al., 2006; Bagatell et al., 2011) and has led to high disease control rates in adult and pediatric patients with ES in a phase II trial (Palmerini et al., 2018).

4.2. Vincristine - Irinotecan

Mascarenhas et al., (Mascarenhas et al., 2010) demonstrated a RR of 30 % among 92 patients with relapsed or recurrent RMS treated with vincristine and irinotecan (Mascarenhas et al., 2010). The same combination has demonstrated superior response rates compared to irinotecan monotherapy as window therapy in newly-diagnosed patients with metastatic RMS (Pappo et al., 2007), while a phase III trial showed that its alternation with VAC (vincristine-dactinomycin-cyclophosphamide) is as efficacious as VAC alone in newly-diagnosed intermediate risk RMS patients and may also reduce long-term toxicity (Hawkins et al., 2014). It has also demonstrated encouraging results against hepatoblastoma (Zhang et al., 2015; Katzenstein et al., 2017). A phase I/II study with vincristine, 5-day irinotecan and an active radiopharmaceutical has led to a RR of 28 % among young patients with advanced neuroblastoma (DuBois et al., 2015). Recently, a study proved efficacy in stage II-IV diffuse anaplastic Wilms' tumor. Of note, patients with stage IV disease achieved a high overall response rate of 79 % and 4-year overall survival rate of 73.7 % (Daw et al., 2020). Ambar et al. (2019), also presented the impressive response of a patient with relapsed desmoplastic small-round cell tumor treated with this regimen Ambar et al. (2019).

4.3. Addition of bevacizumab

The application of antiangiogenics in pediatric solid tumors has been intriguing due to the correlation of the expression of angiogenic factors with poor prognosis (Glade Bender et al., 2011) and also because of the encouraging preclinical results achieved by VEGF inhibition in ES and neuroblastoma (Dalal et al., 2005; Segerstrom et al., 2006). Preclinical evidence that bevacizumab may enhance perfusion of camptothecin agents into neuroblastoma tissue (Dickson et al., 2007) is consistent with the already known synergistic effect of irinotecan and bevacizumab in colon cancer and glioma (Hurwitz et al., 2004; Vredenburgh et al., 2007). Schiavetti et al. (2018), presented 2 consecutive cases with relapsed anaplastic Wilms' tumor that achieved partial response (PR) after treatment with the bevacizumab-irinotecan-vincristine triplet Schiavetti et al. (2018), while a bevacizumab-irinotecan-temozolomide combination has provided responses in recurrent pediatric medulloblastoma (Aguilera et al., 2013).

Based on the above-mentioned evidence and given the fact that vincristine, irinotecan, temozolomide and bevacizumab do not demonstrate overlapping toxicity and may exert synergistic efficacy (Houghton et al., 1995), this multi-drug combination has been mainly studied in

pediatric solid tumors with encouraging results that are more extensively described below.

4.4. VIT (vincristine - Irinotecan - temozolomide)

The VIT regimen is primarily used in refractory or relapsed ES (National Comprehensive Cancer Network, 2020a) and is also a viable option against non-pleomorphic RMS (National Comprehensive Cancer Network, 2020b).

A phase I trial evaluated the toxicity of this regimen in pediatric patients diagnosed with solid tumors, including 4 patients with osteosarcoma, 2 patients with ES, 1 with RMS and 1 with undifferentiated sarcoma. Cefpodoxime was administered for prevention of irinotecan-induced diarrhea. Patients were planned to receive at least two cycles of therapy unless there was disease progression or unacceptable toxicity and to continue up to 12 months. Severe hematologic toxicity was mainly noted in patients with bone marrow involvement at the time of enrollment, or in those that had previously received hematopoietic stem cell transplants or radiotherapy encompassing a significant part of the bone marrow. As far as non-hematologic toxicity was concerned, dose-limiting toxicity was observed only in two patients receiving irinotecan 20 mg/m^2/day. Out of 25 patients, 16 achieved tumor control. One patient with osteosarcoma achieved complete response (CR), but disease progressed after the 4th course, while another patient with RMS achieved CR after the 6th course and was removed from the study in order to proceed to autologous hematopoietic stem cell transplantation. In total 4 out of 8 patients with sarcoma achieved disease control (McNall-Knapp et al., 2010). Retrospective studies of VIT used as salvage chemotherapy for pretreated refractory or relapsed sarcomas in pediatric patients have shown significant rates of disease control (Park et al., 2019). In a relatively recent retrospective study of VIT in pediatric population, 1 out of 12 patients with ES achieved a complete response that lasted 12 months, while overall response rate was 40 % and disease control rate was 80 % in this group of patients. Four out of 8 patients with RMS had stable disease that lasted two to three months, while two out of eight patients with neuroblastoma responded and three more had stable disease. Grade 3–4 diarrhea was seen in 10 % of cases, while both grade 3–4 anemia and grade 3–4 neutropenia occurred in 7.8 % of patients each; grade 3–4 thrombocytopenia occurred in 6.3 % of patients. Of note, 21 out of 34 total patients underwent concurrent local control (Buyukkapu Bay et al., 2019).

Another retrospective study evaluated the effectiveness of this regimen in 22 patients with refractory or relapsed ES (rr-ES). All of them had previously received first line chemotherapy and had either responded poorly or relapsed. In this study patients received high dose irinotecan (50 mg/m^2) on days 1–5, instead of the protracted scheme used in other studies. Control of disease was achieved in 15 out of 22 patients. In particular, five patients achieved a complete response and seven a PR. Four of them continued with high-dose chemotherapy and autologous stem cell transplantation. Responses to VIT and outcome differed according to response to initial therapy. Among nine patients who received VIT after failing to respond to front-line therapy, only two responded (22.2 %), compared to seven of 10 patients (70 %) who received VIT after relapse. Outcome was better for patients with relapsed ES compared with those with disease progression (Raciborska et al., 2013). Given that rr-ES carries a poor prognosis, multiple regimens have been used in that setting in an uncontrolled way with little prospective evidence, no emerging standard of care and no definite chemotherapy backbone proposed, a recent phase II/II international randomized trial evaluated 4 different commonly applied chemotherapy regimens; namely Gemcitabine/Docetaxel (GD) vs Irinotecan/Temozolomide (IT) vs Topotecan/Cyclophosphamide (TC) vs high-dose Ifosfamide (hd-IFO), in patients with relapsed or primary refractory ES (McCabe et al., 2020). The study aimed to identify the optimum between the above chemotherapy regimen in patients with relapsed or primary refractory ES based on the balance between efficacy and toxicity. It applied a multi-arm multi-stage seamless phase II/III "drop-a-loser" Bayesian design with interpretation based on posterior probabilities (with non-informative priors) (McCabe et al., 2020). In the 1 st interim assessment, the GD arm was dropped from further evaluation given the low RR of 11 % observed. In the 2nd interim assessment IT was dropped with a RR of 20 % and hd-IFO vs TC were kept in ongoing evaluation after demonstrating a 21 % RR. However, it can be said that with this type of sequential drop-out design, 38 % of patients randomized to either hd-IFO or TC vs 27 % of patients randomized to IT discontinued treatment to the allocated regimen (McCabe et al., 2020).

Mixon et al., (Mixon et al., 2013) presented a case of a heavily pretreated patient treated with VIT for metastatic RMS who achieved a complete response which lasted for 27 weeks, while three other patients progressed at the first scheduled screening (Mixon et al., 2013). There is also implication that MGMT methylation can be used as predictive marker of response to TMZ in these patients (Tolcher et al., 2003; Kinoshita et al., 2018). A retrospective study by Winter et al., (Winter et al., 2015) demonstrated a response rate of 43 % with VIT in patients with relapsed RMS after first line chemotherapy with various regimens and different approaches for local disease control (Winter et al., 2015). In a recent phase II clinical study, the addition of temozolomide to vincristine and irinotecan led to statistically significant improved ORR (44 % vs 31 %), PFS and OS comparable to vincristine and irinotecan alone in young and adult patients diagnosed with relapsed or refractory RMS (Defachelles et al., 2019).

A recent study by Liu et al., (Liu et al., 2020) explored the effectiveness of VIT regimen in six pediatric patients with desmoplastic small round cell tumor (DSRCT). Three out of six patients achieved tumor response by RECIST 1.1 criteria for solid tumors, after two cycles of VIT. After chemotherapy, all patients underwent surgical resection and radiotherapy, while two received intraperitoneal chemotherapy at the time of surgery. In total, four patients completed therapy, and three of them remained disease-free at a median follow-up of 46.7 months. Most common toxicities in this study were gastrointestinal and hematologic, in accordance to the known toxicity profile from other studies (Liu et al., 2020).

4.5. VITb (vincristine - irinotecan - temozolomide - bevacizumab)

There is still no consensus regarding the systematic use of VITb regimen in medical oncology, as it has not been widely studied. Phase I studies have established that this regimen is well tolerated in pediatric patients. These clinical trials initially included patients with different types of solid tumors, including soft tissue sarcomas, Wilms' tumor and bone sarcomas.

In one study by Venkataramani et al., (Venkatramani et al., 2013) 12 pediatric patients with solid tumors (6 sarcomas of various histologies, 3 Wilms' tumors, 1 medulloblastoma, 2 hepatocellular carcinomas) were recruited. Disease control was achieved in 5 out of 6 patients with sarcomas, while 2 out of 3 patients diagnosed with Wilms' tumor achieved CR and the other one had PR and the only patient with medulloblastoma had also PR. This regimen showed no severe hematological toxicity, while common adverse effects like diarrhea were symptomatically controlled (Venkatramani et al., 2013).

Another phase I study by Wagner et al., (Wagner et al., 2013) tested the VOITb (Vincristine, oral Irinotecan, Temozolomide, Bevacizumab) regimen which consisted of irinotecan 90 mg/m^2/day on days 1–5 per os, temozolomide 150 mg/m^2/day per os on days 1–5, vincristine 1,5 mg/m^2 (max2 mg) iv day 1, bevacizumab 15 mg/kg (maximum dose 800 mg) day 1. Cefixime 8 mg/kg daily (maximum 400 mg) was administered for 10 days starting 2 days before each cycle of chemotherapy prophylactically against irinotecan-induced diarrhea. Each course was administered every 21 days, for a total of 6 cycles. 13 patients with relapsed disease enrolled in this study, including 2 patients with ES, 1 with RMS, 1 with hepatocellular carcinoma, 1 with Wilms' tumor, 2 with neuroblastoma, as well as 2 with glioma. Both patients

Table 1
Overview of responses and toxicity of VIT and VIT-b regimens in various solid tumors.

Tumor	Median age (yo)	ORR (%)	DCR	PFS (m) or (% at x years)	OS (m) or (% at y years)	Regimen	Toxicities	Study
Rhabdomyo-sarcoma (RMS)	12 (1–22)*	0 % (0/1)	0% (0/1)	na	na	V: 1.5 mg/m2 d1 I: 90 mg/m2 po d1-d5 T: 100–150 mg/m2 iv d1-d5 B: 15 mg/kg iv d1	gr 4 Neutropenia gr 3 Gastrointestinal disorders*	(Wagner et al., 2013)
	18.5 (2–40)*	0 % (0/8)	50 % (4/8)	na (PFSR: 33.8 % at 1 y)*	na (OSR: 45.5 % at 2 y)*	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 100 mg/m2 po d1–5	gr 4 Neutropenia gr 3 Colitis*	(Park et al., 2019)
	1–21	44 % (24/55)	na	na	na	V: 1.5 mg/m2 iv d1 + d8 I: 50 mg/m2 iv d1-d5 T: 125 mg/m^2 po d1-d5 (150 mg/m^2 from cycle 2 if no > grade 2 toxicity)	Hematologic toxicity	(Defachelles et al., 2019)
	10 (1–17)*	0% (0/8)	50 % (4/8)	16 (9–63)	6 (1–10)	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 150 mg/m2 iv d1-d5	Diarrhea Hematologic toxicity*	(Buyukkapu Bay et al., 2019)
	9.6 (2–20)*	100 % (1/1)	100 % (1/1)	na	na	V: 1.5 mg/m2 iv d1–5 I: 15–20 mg/m2 iv d1–5 + d8–12 T: 100 mg/m2 po d1–5	gr 3 / 4 Hematologic toxicity*	(McNall-Knapp et al., 2010)
	8 (2-17)	0% (0/15)	26.7% (4/15)	16 (2.8–45)	na	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv or 70–100 mg/m2 po d1-d5 T: 100–150 mg/m2 po d1-d5	na	(Setty et al., 2018)
	up to 18	42% (3/7)	100 % (7/7)	na	na	na	na	(Winter et al., 2015)
	11 (10–13)	25 % (1/4)	25 % (1/4)	6.5	na	V: 1.5 mg/m2 iv d1+d8 I: 30 mg/m2 iv d1-d5 T: 100 mg/m2 po d1-d5	gr 2 Neurotoxicity gr 2 Infection	(Mixon et al., 2013)
	14.3	54% (12/22)	68 % (15/22)	3	26.9% at 2 yrs	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 125 mg/m2 po d1-d5	Hematologic toxicity Diarrhea	(Raciborska et al., 2013)
	10 (1–17)*	40 % (6/15)	80 % (12/15)	6 (2–11)	30.9 % at 2 yrs*	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 150 mg/m2 iv d1-d5	Hematologic toxicity Diarrhea*	(Buyukkapu Bay et al., 2019)
	18.5 (2–40)*	50 % (1/2)	100 % (2/2)	na (PFS-R 33.8 % at 1 yr)*	na (OS-R: 45.5 % at 2 yrs)*	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 100 mg/m2 po d1–5	gr 4 Neutropenia gr 3 Colitis*	(Park et al., 2019)
Ewing Sarcoma	11 (4–19.5)*	0% (0/1)	100 % (1/1)	na	na	V: 1.5 mg/m2 iv d1+d8 I: 30 or 50 mg/m2 iv d1-d5 T 100 mg/m2 d1-d5 po B: 15 mg/kg d1	gr 3 Hematologic Toxicity Colitis Hyperbilirubinemia*	(Venkatramani et al., 2013)
	12 (1–22)*	100 % (2/2)	100 % (2/2)	na	na	V: 1.5 mg/m^2 d1 I: 90 mg/m^2 po d1-d5 T: 100–150 mg/m^2 iv d1-d5 B: 15 mg/kg iv d1	gr 4 Neutropenia gr 3 Gastrointestinal disorders*	(Wagner et al., 2013)
	21 (3–65)	34 % (17/51)	71 % (36/51)	3.9 (1–29)	na (55 % at 1 yr)	I: 40 mg/m^2 iv d1-d5 T 100 mg/m^2 d1-d5 po	Gr 3–4 neutropenia (12%) diarrhea (4%)	(Palmerini et al., 2018)
	10 (1–17)*	50 % (1/2)	50 % (1/2)	6*	30.9 % at 2 y*	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 150 mg/m2 iv d1-d5	Hematologic toxicity Diarrhea*	Bay 2019 (Buyukkapu Bay et al., 2019)
Osteosarcoma	11 (4–19.5)*	0% (0/2)	50 % (1/2)	na	na	V: 1.5 mg/m2 iv d1+d8 I: 30 or 50 mg/m2 iv d1-d5 T 100 mg/m2 d1-d5 po B: 15 mg/kg d1	gr 3 Hematologic toxicity Colitis Hyperbilirubinemia*	(Venkatramani et al., 2013)
	9.6 (2–20)*	25 % (1/4)	50 % (2/4)	na	na	V: 1.5 mg/m2 iv d1–5 I: 15–20 mg/m2 iv d1–5 d8–12 T: 100 mg/m2 po d1–5	gr 3 / 4 Hematologic toxicity*	(McNall-Knapp et al., 2010)
	18.5 (2-40)*	14 % (1/7)	43 % (3/7)	na (PFSR: 33.8% at 1 y)*	na (OSR: 45.5% at 2 y)*	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 100 mg/m2 po d1–5	gr 4 Neutropenia gr 3 Colitis	(Park et al., 2019)
Wilms tumor	10 (1–17)*	0% (0/1)	100 % (1/1)	4	30.9 % at 2 y*	V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 150 mg/m2 iv d1-d5	Hematologic toxicity Diarrhea*	(Buyukkapu Bay et al., 2019)
	11 (4–19.5)*	100 % (3/3)	100 % (3/3)	na	na	V: 1.5 mg/m2 iv d1+d8	gr 3 Hematologic toxicity	(Venkatramani et al., 2013)

(continued on next page)

Table 1 (*continued*)

Tumor	Median age (yo)	ORR (%)	DCR	PFS (m) or (% at x years)	OS (m) or (% at y years)	Regimen	Toxicities	Study
	12 (1–22)*	0% (0/1)	0% (0/1)	na	na	I: 30 or 50 mg/m2 iv d1-d5 T 100 mg/m2 d1-d5 po B: 15 mg/kg d1 V: 1.5 mg/m2 d1 I: 90 mg/m2 po d1-d5 T: 100–150 mg/m2 iv d1-d5 B: 15 mg/kg iv d1 V: 1.5 mg/m2 iv d1+d8	Colitis Hyperbilirubinemia* gr 4 Neutropenia gr 3 Gastrointestinal disorders* gr 3	(Wagner et al., 2013)
Medulloblastoma	11 (4–19.5)*	100 % (1/1)	100 % (1/1)	na	na	I: 30 or 50 mg/m2 iv d1-d5 T 100 mg/m2 d1-d5 po B: 15 mg/kg d1 V: 1.5 mg/m2 iv d1 (2 mg max)	Hematologic Toxicity Colitis Hyperbilirubinemia*	(Venkatramani et al., 2013)
Gliomas								
Glioblastoma multiforme	31	100 % (1/1)	100 % (1/1)	na	na	I: 30 mg/m2 iv (escalated to 50 mg/m2) d1-d5 T: 100 mg/m2 po d1–5 B: 15 mg/kg iv d1 V: 1.5 mg/m2 iv d1–5	gr 4 Hepatotoxicity	(Papageorgiou et al., 2020)
Gliomas (brainstem glioma, ependymoma)	9.6 (2–20)*	0% (0/5)	80 % (4/5)	na	na	I: 15–20 mg/m2 iv d1–5 d8–12 T: 100 mg/m2 po d1–5 V: 1.5 mg/m2 d1	gr 3 / 4 Hematologic toxicity* gr 4 Neutropenia	(McNall-Knapp et al., 2010)
glioblastoma multiforme, ependymoma	12 (1–22)*	0% (0/2)	100 % (2/2)	na	na	I: 90 mg/m2 po d1-d5 T: 100–150 mg/m2 iv d1-d5 B: 15 mg/kg iv d1 V: 1.5 mg/m2 iv d1	gr 3 Gastrointestinal disorders* Hematologic toxicity	(Wagner et al., 2013)
	10 (1–17)*	25 % (2/8)	63 % (5/8)	3	30.9 % at 2 y*	I: 50 mg/m2 iv d1-d5 T: 150 mg/m2 iv d1-d5	Diarrhea*	(Buyukkapu Bay et al., 2019)
Neuroblastoma	9.6 (2–20)*	33 % (1/3)	100 % (3/3)	na	na	V: 1.5 mg/m2 iv d1–5 I: 15–20 mg/m2 iv d1–5 d8–12 T: 100 mg/m2 po d1–5	gr 3 / 4 Hematologic toxicity*	(McNall-Knapp et al., 2010)
	12 (1–22)*	0% (0/2)	100 % (2/2)	na	na	V: 1.5 mg/m2 d1 I: 90 mg/m2 po d1-d5 T: 100–150 mg/m2 iv d1-d5 B: 15 mg/kg iv d1	gr 4 Neutropenia gr 3 Gastrointestinal disorders*	(Wagner et al., 2013)
	11 (4–19.5)*	50 % (1/2)	100 % (2/2)	na	na	V: 1.5 mg/m2 iv d1+d8 I: 30 or 50 mg/m2 iv d1-d5 T 100 mg/m2 d1-d5 po B: 15 mg/kg d1	gr 3 Hematologic Toxicity Colitis Hyperbilirubinemia*	(Venkatramani et al., 2013)
Hepatocellular carcinoma	11 (4–19.5)*	0% (0/1)	100 % (1/1)	na	na	V: 1.5 mg/m2 d1 I: 90 mg/m2 po d1-d5 T: 100–150 mg/m2 iv d1-d5 B: 15 mg/kg iv d1	gr 4 Neutropenia gr 3 Gastrointestinal disorders*	(Wagner et al., 2013)
	9.6 (2–20)*	0% (0/1)	0% (0/1)	na	na	V: 1.5 mg/m2 iv d1–5 I: 15–20 mg/m2 iv d1–5 d8–12 T: 100 mg/m2 po d1–5	gr 3 / 4 Hematologic toxicity*	(McNall-Knapp et al., 2010)
	9.6 (2–20)*	0% (0/4)	75 % (3/4)	na	na	V: 1.5 mg/m2 iv d1–5 I: 15–20 mg/m2 iv d1–5 d8–12 T: 100 mg/m2 po d1–5	gr 3 / 4 *	(McNall-Knapp et al., 2010)
Hepatoblastoma								
	12 (1–22)*	0% (0/1)	100 % (1/1)	na	na	V: 1.5 mg/m2 d1 I: 90 mg/m2 po d1-d5 T: 100–150 mg/m2 iv d1-d5 B: 15 mg/kg iv d1	gr 4 Neutropenia gr 3 *	(Wagner et al., 2013)
Desmoplastic small round cell tumor (DSRCT)	15.1 (3.2–16.4)	50 % (3/6)	100 % (6/6)	na (75 % at 2 years)	na (75 % at 2 years)	Neoadjuvant VIT (2 cycles) V: 1.5 mg/m2 iv d1 I: 50 mg/m2 iv d1-d5 T: 100 mg/m2 po d1-d5 +Surgery +Radiation therapy	Hematologic toxicity Gastrointestinal disorders (including, *C. difficile* infection)	(Liu et al., 2020)

Summary of current literature of combination of Vincristine with Irinotecan and Temozolomide (VIT), with or without the addition of Bevacizumab (VITb) : vincristine, I: irinotecan, T: temozolomide, B: bevacizumab, po: per os, iv: intravenous, na: not available, yo: years old, m: months, y: years, ORR: overall response rate

PFS: progression free survival, PFSR: progression free survival rate, DCR: disease control rate, OS: overall survival OSR: overall survival rate, gr: grade. *The study includes patients with other diagnoses and no specific information regarding age, PFS and OS is provided separately.

with ES received 6 courses of chemotherapy and had an objective response. The first patient entered in the study had multifocal bone metastases and experienced a CR at the end. The second patient presented with an extra-osseous mass from a pubic bone metastasis and demonstrated a PR. In this study temozolomide was associated with significant myelosuppression, so a dose adjustment to 100 mg/m^2 was necessary for the three patients who completed the study (Wagner et al., 2013) (Table 1).

Furthermore, we recently reported a case regarding a young patient with GBM that was treated with VITb for second relapse after 2 surgical resections and chemo-radiotherapy courses with temozolomide at our institution (Papageorgiou et al., 2020). The patient achieved a PR with clinical improvement after the 4th course and proceeded to complete 8 courses of the regimen. He was later put on bevacizumab maintenance and continues without progression 10 months after the second relapse and 4 years after initial diagnosis. The only adverse event was hepatotoxicity that was attributed to dexamethasone and temozolomide (Sarganas et al., 2012; Grant et al., 2013; Miller et al., 2012) and is constantly improving during bevacizumab maintenance and after the switch from dexamethasone to hydrocortisone. Currently there is no other patient with GBM that has responded to VIT or VITb to our knowledge, so we firmly believe that a relevant clinical study should be conducted in patients with relapsed GBM.

5. Conclusion

We encourage further investigation regarding the effectiveness of VIT and VITb regimens in pediatric and young adult patients with refractory or relapsed solid tumors, as they have already been successful in treating ES and non-pleomorphic RMS and they seem to be promising and offering satisfactory disease control rates in osteosarcoma, Wilms' tumor, hepatocellular carcinoma, CNS tumors, neuroblastoma and hepatoblastoma. VIT and VITb hold a manageable toxicity profile, including mainly neutropenia, thrombocytopenia and diarrhea; the latter is well controlled with prophylactic antibiotic use.

Financial Disclosure

None declared.

Declaration of Competing Interest

None declared.

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