Biologics: Targets and Therapy

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REVIEW

Monoclonal Antibody Therapies for High Risk Neuroblastoma

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Abstract: Monoclonal antibodies (mAbs) are part of the standard of care for the treatment of many adult solid tumors. Until recently none have been approved for use in children with solid tumors. Neuroblastoma (NB) is the most common extracranial solid tumor in children. Those with high-risk disease, despite treatment with very intensive multimodal therapy, still have poor overall survival. Results of treatment with an immunotherapy regimen using a chimeric (human/mouse) mAb against a cell surface disialoganglioside (GD2) have changed the standard of care for these children and resulted in the first approval of a mAb for use in children with solid tumors. This article will review the use of the various anti-GD2 mAbs in children with NB, methods that have been or are being evaluated for enhancing their efficacy, as well as review other promising antigenic targets for the therapeutic use of mAbs in children with NB.

Keywords: immunotherapy, neuroblastoma, anti-disialoganglioside, anti-GD2, chimeric, effector cells

Introduction

Monoclonal antibodies (mAbs) have developed into effective therapies for many adult malignancies. The global market for mAbs to treat cancer was estimated to be at more than 40 billion dollars in 2019 and likely to grow to more than 70 billion by 2024 (https://www.marketdataforecast.com/market-reports/global-cancer-monoclonal-antibodies-market). Monoclonal antibodies kill cancer cells in several different ways: inhibiting cancer cell signaling,[1–3] stimulating immune effector cells to destroy tumor cells (antibody-dependent cell-mediated cytotoxicity; ADCC),[4] by fixing complement (complement-dependent cytotoxicity; CDC), resulting in assembly of a membrane attack complex and cell lysis (Figure 1),[4] and by stimulating adaptive immunity.[5] Other antibodies can cause changes in the tumor vasculature, resulting in improved treatment response.[6] They have also been used as targeting agents by being coupled to toxic payloads such as drugs,[7,8] toxins[9] or radioisotopes (Figure 1).[10,11] More recently mAbs have also been used to target cells in the tumor microenvironment resulting in enhanced anti-tumor immune responses.[4,12]

Neuroblastoma (NB) is the most common extracranial solid tumor in children and is thought to be derived from primitive neural crest cells.[13] It can manifest anywhere along the sympathetic nervous system, with an adrenal mass being the most common primary site.[14,15] "High-risk" NB is largely defined by patients older than 18 months of age at presentation with widely metastatic disease.[16] Despite intensive multimodal treatment, more than half of these patients still die of their

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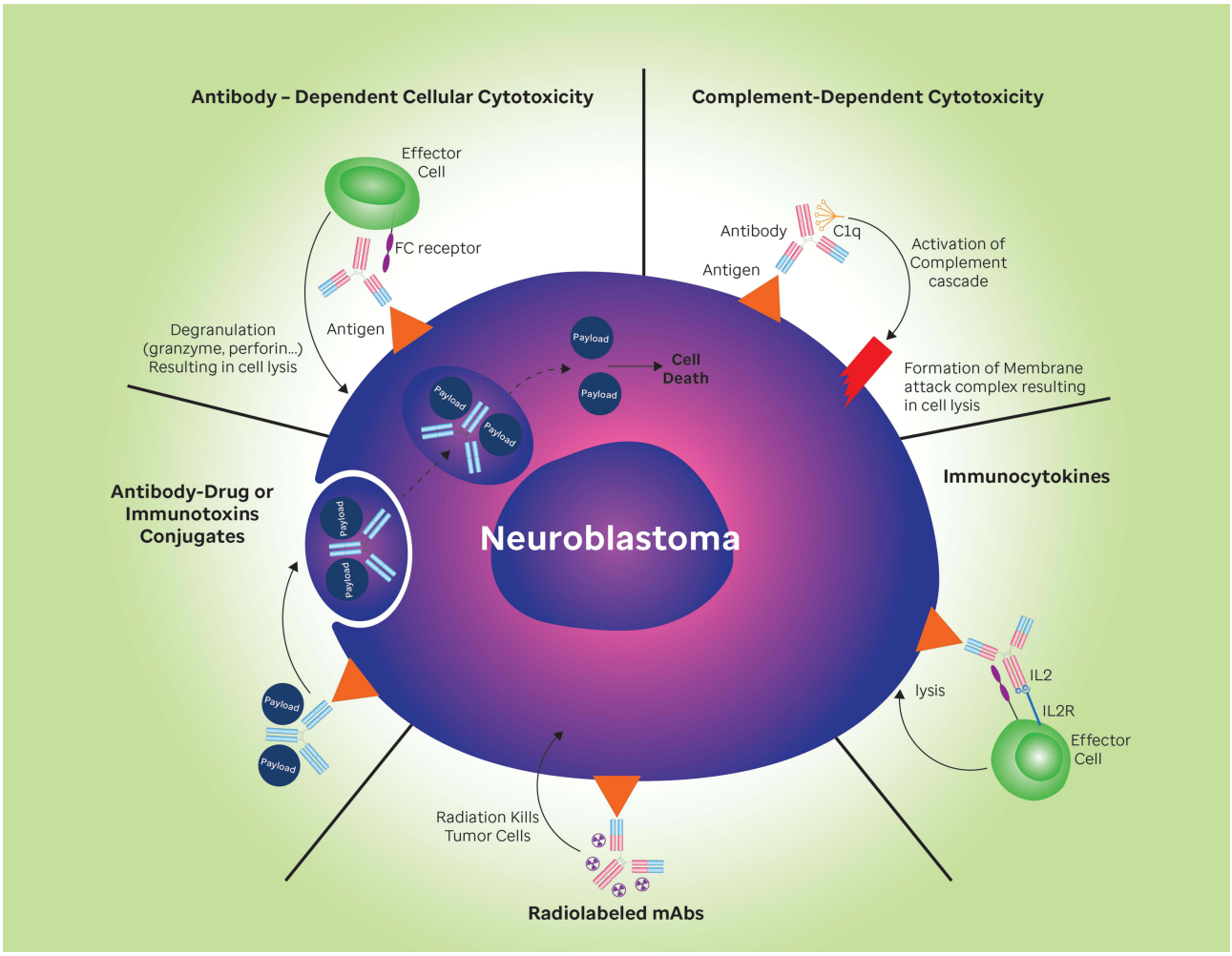

Figure 1 Antitumor mechanisms of GD2 antibodies and antibody conjugates. Solid triangle represents disialoganglioside (GD2) on cell surface.

disease.[17] In the 1980s it was discovered that neuroblasts almost uniformly express disialoganglioside (GD2) on their surfaces and this was used as a target to make several monoclonal antibodies, two of which have now been approved for use by the FDA[18–25] (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-naxitamab-high-risk-neuroblastoma-bone-or-bone-marrow) and another approved by the European Medicines Agency (https://www.ema.europa.eu/en/medicines/human/EPAR/qarziba#:~:text=The%20European%20Commission%20granted%20a,Qarziba%20on%2027%20November%202017). The major anti-tumor mechanism of the anti-GD2 mAbs is likely ADCC mediated by NK cells[26] and to a lesser extent neutrophils and macrophages.[27,28] This article will review the use of the anti-GD2 mAbs in children with NB, methods that have been or are being evaluated for enhancing their efficacy, as well as review other promising antigenic targets for the therapeutic use of mAbs in children with NB.

Immunotherapeutic Targets of Neuroblastoma

Disialoganglioside (GD2)

Characteristics of antigens that make them attractive for mAb based therapy include consistent expression on the target cancer cells and limited expression on normal cells. One such antigen on neuroblasts is the disialoganglioside, GD2.[19] While it is uniformly expressed on neuroblasts,[19,20,29,30] in normal tissues it is expressed only on peripheral and central nerve fibers,[31] mesenchymal stem cells,[32,33] melanocytes[34] and lymphocytes.[31,35,36] It appears to have a role in attachment of tumor cells to the extracellular matrix,[37] as well as effects on cell invasion and proliferation.[29] Anti-GD2 mAbs that have been used

clinically are summarized in Table 1. The first to be evaluated in the clinic were the murine antibodies 3F8 and 14G2a. Common acute toxicities to anti-GD2 mAbs include fever, hypotension, neuropathic pain and capillary leak syndrome (see Table 1). The fever and hypotension are likely related to allergic reactions to murine protein and pain due to mAb binding to GD2 positive peripheral nerves and subsequent complement activation.[38,39] Capillary leak was more common during courses administered with interleukin-2 (IL-2) in the large randomized trial of dinutuximab[25] and may be mostly related to systemically administered IL-2 or endogenous IL-2 produced in response to anti-GD2 mAb administration.[40,41]

Murine Anti-GD2 Antibodies

3F8

This murine IgG3 mAb specific for GD2,[30] kills tumor cells by ADCC[42] and by activating complement.[30] It has been studied extensively in patients as a single agent[21,43] and in combination with other agents used to enhance ADCC, such as GM-CSF[42,44,45] and β-glucan (NCT00492167).[46] There were some responses in patients with small amounts of bone and/or marrow disease but no responses in those with bulky disease.[44,47–49] Human anti-mouse antibodies (HAMA) developed in a majority of patients treated with 3F8.[49–52]

14G2a

This murine antibody is an isotype switch variant of the murine IgG3 14.18 anti-GD2 mAb. Because it had improved ADCC compared to 14.18, 14G2a was chosen for clinical evaluation.[22] Two trials treated 27 patients at dosages from 50 to 400mg/m^2.[23,53] It was tolerated but with significant side effects (summarized in Table 1) and some modest anti-tumor activity. Human anti-mouse antibodies (HAMA) developed in 25/27 patients.[23,53] In an attempt to enhance ADCC it was combined with interleukin-2 in another Phase I study. Thirty-three patients were enrolled, 31 with NB. Pain and allergic reactions were common. Nine of 21 evaluable children developed HAMA.[54]

Because murine antibodies result in allergic reactions and the development of HAMA, accelerating the clearance of the antibodies and reducing their antitumor effects,[55] techniques to make antibodies "more human" have been developed.[56] Figure 2 depicts the general structure of antibodies and their engineering modifications which have been utilized to make them more tolerable.

Chimeric Anti-GD2 Antibodies

Dinutuximab (Ch14.18)

To begin to address the immunogenic properties of murine anti-GD2 antibodies, the human Fc constant regions of an IgG1 immunoglobulin was fused with the Fab portion of the murine 14G2a antibody to produce this chimeric mouse/human antibody against GD2 (Figure 2). In vitro, ch14.18 mediated ADCC 50–100 fold more efficiently than 14.G2A,[57] and was tested extensively in the clinic as a single agent and with cytokines GM-CSF and IL-2.[58–67] In 2010, Yu et al of the Children's Oncology Group (COG) reported on a randomized Phase 3 trial of ch14.18, in newly diagnosed children with high-risk NB who had achieved at least a partial response to induction chemotherapy. Following myeloablative chemotherapy, in a state of minimal residual disease, patients then received dinutuximab qd x 4 every 28 days given with either GM-CSF (course 1, 3 and 5) or interleukin-2 (IL-2; course 2 and 4) as well as monthly isotretinoin.[25] This immunotherapeutic combination resulted in a dramatic improvement in 2-year event-free survival, compared to the group who received isotretinoin alone (66% vs 46% at 2-yrs, respectively; P = 0.01). These data led to NB becoming the first pediatric solid tumor with an approved immunotherapy, using this mAb, now called dinutuximab (Unituxin®), in combination with cytokines and isotretinoin (https://www.cancer.gov/news-events/cancer-currents-blog/2015/dinutuximab-neuroblastoma). These excellent results with dinutuximab provide promise that further improvements in immunotherapy will enhance outcome in children with NB. For example, the use of dinutuximab in combination with irinotecan and temozolomide has shown significant activity in patients with relapsed/refractory disease with objective responses in 22/53 patients (41.5%; 95% CI 28.2–54.8%).[68,69] Ongoing studies extending the evaluation of dinutuximab in neuroblastoma include COG studies ANBL1821, a randomized Phase II study of irinotecan, temozolomide and dinutuximab with/without eflornithine (NCT03794349), ANBL07P1, a pilot study in newly diagnosed children adding dinutuximab to induction chemotherapy (NCT03786783) and ANBL19P1, a Pilot study of dinutuximab, GM-CSF and isotretinoin with irinotecan and temozolomide in the post-consolidation setting (NCT04385277). The NANT

Table 1 Clinical Trials of Anti-GD2 Monoclonal Antibodies

Antibody		Characteristics	Other Key Features	Dosage	Common Toxicities	References
Approved						
ch14.18 (Dinutuximab, Unituxan®)	Approved by FDA*	Murine-human IgG1 mAb produced in murine myeloma SP2/0 cells	Only difference between dinutuximab and dinutuximab beta is the glycosylation pattern which is a result of manufacture in different cell lines	17.5 mg/m^2/qd x 4	Neuropathic pain, capillary leak, hypotension, hypersensitivity reactions	[25]
ch14.18/CHO (dinutuximab beta; Qarziba®)	Approved by EMA**	Murine-human IgG1 mAb made in CHO cells		100 mg/m^2/course: either 10 mg/m^2/d x10 d or 20 mg/m^2/d x 5 d	Neuropathic pain, capillary leak, hypersensitivity reactions, "impaired general condition"	[73,74]
Hu3F8 (Naxitumab)	Approved by FDA†	Humanized 3F8 mAb	IgG1 humanized form of m3F8	0.9–9.6 mg/kg/cycle [M, W,Fri q mo] (27–288 mg/m^2)	Pain, urticaria and cough	[81,82]
Investigational						
3F8		Murine IgG3 mAb	HAMA interferes with activity	5–100 mg/m^2 iv over 8hrs x 2–4 d	Pain, focal urticaria, hypertension	[21,55]
14.G2a		Murine IgG2a mAb	HAMA interferes with activity[157]	50–400 mg/m^2 ci x 5–10 d	Neuropathic pain, hypertension, fever, rash, urticaria, pruritus, paresthesia, weakness, chronic refractory postural hypotension	[23,53]
Hu14.18K322A		Humanized IgG1 mAb with point mutation designed to decrease complement activation	ADCC activity may be more robust than dinutuximab and may cause less pain	2–70 mg/m^2 qd x 4	Neuropathic pain, cough, asthenia, sensory neuropathy, anorexia, serum sickness, hypertensive encephalopathy	[39,77,78]
Antibody Conjugates						
^{131}I-3F8		Murine mAb attached to ^{131}I		1 −20 mCi	Headache, fever and vomiting	[11,158]

(*Continued*)

Table 1 (Continued).

Antibody		Characteristics	Other Key Features	Dosage	Common Toxicities	References
Hu14.8-IL-2		Humanized 14.18 attached to Interleukin-2	Patients with disease evaluable only by MIBG and/or BM histology had better responses than those with bulky disease	2–14.4 mg/m^2/d	Hypotension, capillary leak, fever, hypoxia, rigors, blurred vision, allergic reaction, elevated transaminases and bilirubin, neutropenia, thrombocytopenia	[101,102]

Notes: *https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125516Orig1s000TOC.cfm; indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy.[25] **https://www.ema.europa.eu/en/medicines/human/EPAR/qarziba; indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. †https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-naxitamab-high-risk-neuroblastoma-bone-or-bone-marrow.

Abbreviations: qd, daily; d, day; ADCC, antibody-dependent cell-mediated cytotoxicity; HAMA, human anti-mouse antibodies.

consortium is also evaluating dinutuximab in combination with Vorinostat and ^{131}I-MIBG (NCT03332667).

Dinutuximab-Beta

A biosimilar to dinutuximab, ch14.18/CHO, now called dinutuximab beta (Qarziba®), has been approved by the European Medicines Agency.[70] Ch14.18 was recloned in Chinese hamster ovary (CHO) cells[26] and shown to have comparable pharmacokinetics and safety profile to dinutuximab.[71] The International Society of Pediatric Oncology Europe Neuroblastoma group (SIOPEN) was evaluating dinutuximab beta in a randomized trial (HR-NBL1),

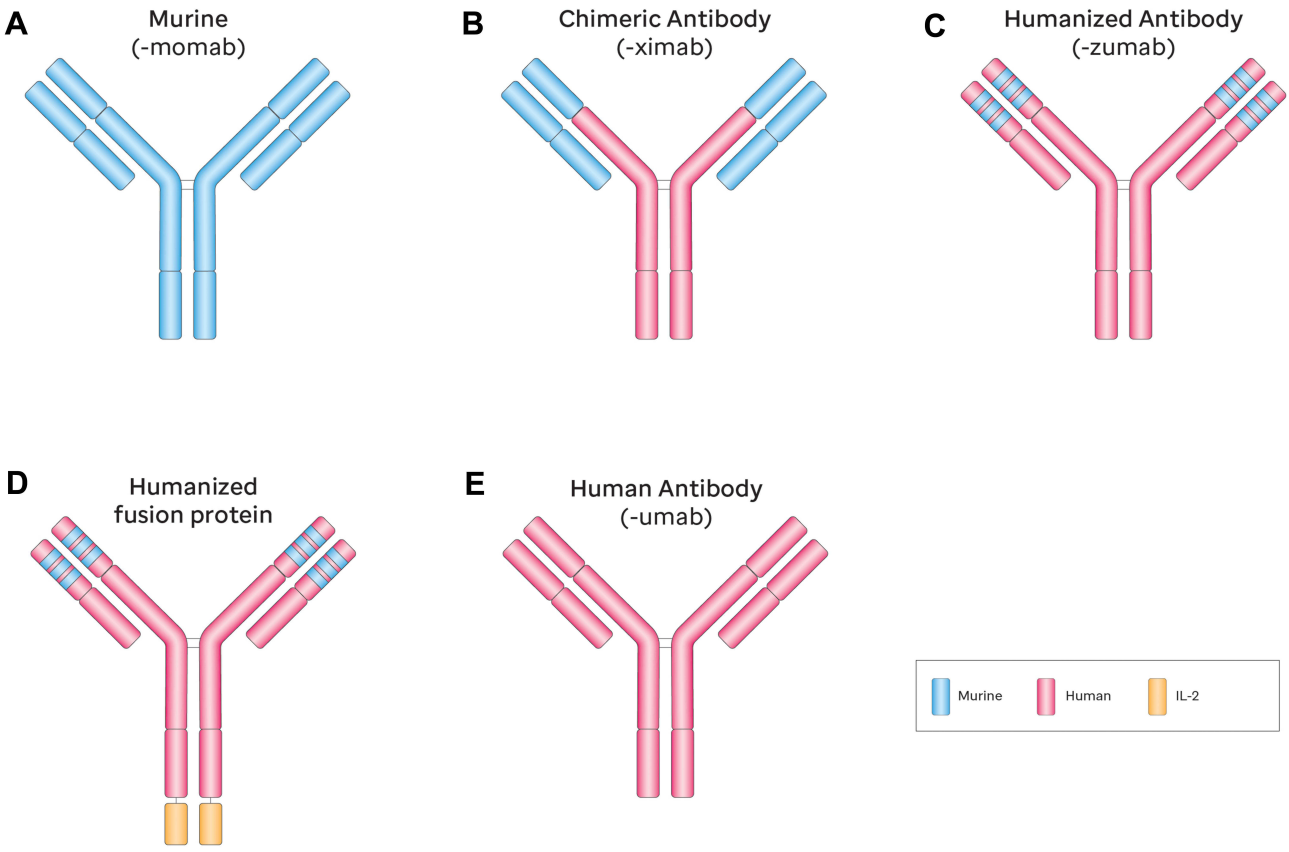

Figure 2 Schematic diagram of anti-GD2 monoclonal antibodies and naming schema based on structure. A-fully murine monoclonal antibody, B-chimeric monoclonal antibody, C-humanized monoclonal antibody, D-humanized monoclononal antibody with addition of interleukin-2, and E-fully human monoclonal antibody. Suffix of murine mAbs -momab, suffix of chimeric antibodies - ximab; suffix of humanized antibodies – zumab; suffix of human antibodies – umab.

comparing it to isotretinoin alone, until results of COG's trial with dinutuximab[25] became available, after which accrual was halted and the design was modified to investigate the role of dinutuximab beta with/without IL-2.[72,73] This randomized study concluded that there were higher rates of fever, pain, allergic reactions and other toxicities when dinutuximab beta was combined with IL-2. Additionally there was no evidence that IL-2 improved outcomes.[73] Based on these data, IL-2 is no longer used with dinutuximab in the ongoing COG trial for children with newly diagnosed high-risk NB (ANBL1531; NCT03126916).

To improve the tolerability of dinutuximab beta, a 10-day continuous infusion schedule was developed. Fifty-three patients received 10 mg/m^2/day of dinutuximab beta by 24-hr continuous infusion daily x 10 with 6×10^6 IU/m^2 IL-2 (d1–5; 8–12) with oral isotretinoin. They found low pain scores and reduced IV morphine usage with subsequent cycles, allowing mAb infusions as outpatients in more than 90% of cycles after the first course.[74] This long-term infusion schedule of dinutuximab beta is being evaluated further in newly diagnosed children by the SIOPEN group, in combination with/without 3×10^6 IU/m^2 IL-2 (d1–5; 8–12), which is 50% of the IL-2 dose used in previous randomization (NCT01704716).[73] Dinutuximab beta is also being further evaluated by the Innovative Therapies for Children with Cancer in Europe consortium in a randomized trial in children with relapsed/refractory neuroblastoma in combination with chemotherapy (BEACON-Immuno) and in another consortium, in combination with nivolumab and ^{131}I-MIBG (NCT02914405).

Humanized Anti-GD2 Antibodies

Hu14.18K322A

Humanization of murine mAbs makes them less immunogenic and more tolerable.[75] This mAb contains fully human amino acid sequences for the IgG1 kappa light and heavy chains, combined with the complementarity-determining regions of antigen binding of the murine 14.18. The result is an approximately 98% human mAb. Additionally, a single point mutation was introduced to decrease complement activation (K322A)[76] in an attempt to ameliorate the severe neuropathic pain[39] seen with all anti-GD2 mAbs (see Table 1). As a single agent hu14.18K322A was given in doses of 2–70 mg/m^2/d x 4, q 28 days. Toxicities were similar to other anti-GD2 mAbs, including significant pain, especially with the first course.[77] However, in a retrospective review comparing pain outcomes of nine newly diagnosed children treated with dinutuximab (25 mg/m^2/d x 4, given over 10 hours daily x 4) to nineteen patients with recurrent NB being treated on the Phase 1 trial of hu14.18K322A (dosages of 40, 50, 60 or 70 mg/m^2/d x 4, given over 4-hrs daily x 4),[77] those receiving hu14.18K322A had lower opioid requirements than the nine who were receiving dinutuximab.[78] Furthermore, the differences in median opioid requirements for the overall course were significantly lower (1.57 vs 2.41 mg/kg; $p = 0.019$).[78] This reduction in opioid support for those children receiving hu14.18K322A was despite receiving mAb doses more than 1.5 times the dose of dinutuximab, strongly suggesting that the K322A mutation was effective in reducing, but not eliminating the pain experienced by all anti-GD2 mAbs. Hu14.18K322A was combined with each of six courses of induction chemotherapy in a Phase II study involving 64 patients 19 years or younger with newly diagnosed high-risk NB. Each course of "chemoimmunotherapy" was followed by daily sq GM-CSF and 1 x 10-^{6}IU/m^2 of IL-2 every other day for six doses. Some patients received an additional course of hu14.18K322A along with infusion of parental natural killer (NK) cells during the consolidation phase of treatment. Following recovery from consolidation, minimal residual disease was treated with GM-CSF, IL-2 and isotretinoin, identical to Yu et al,[25] with the substitution of hu14.18K322A for dinutuximab.[79] In this single center Phase II trial, adding hu14.18K322A to induction chemotherapy produced early partial response (PR) or better in most patients, resulted in no progressions during induction, improved Curie Scores[80] at the end of induction, and yielded an encouraging 2-year event-free survival (EFS) of 82.6% (95% CI, 70.1–90.3%).[79] These data supported the development of a multi-institutional pilot study of dinutuximab given with induction chemotherapy by the COG (ANBL07P1; NCT03786783) which has just completed accrual.

Hu3F8

To circumvent the problem of HAMA development which accelerates antibody clearance, compromises efficacy and in some patients prevents retreatment, a humanized IgG1 form of the murine anti-GD2 mAb 3F8 (Hu3F8) was created.[81] Now called naxitamab (DANYELZA®), in a Phase I trial, 57 patients were treated in the outpatient setting. Cohorts of 3 to 6 patients per dose level were enrolled. Naxitamab was given in doses from 0.9 to 9.6 mg/kg/cycle by 30-minute IV infusion on Monday,

Wednesday, and Friday as well as GM-CSF, sq from day −5 through the last naxitamab infusion. As with other anti-GD2 mAbs, manageable neuropathic pain was seen in most patients.[82] Humanized 3F8, (naxitamab), was granted Breakthrough Therapy designation in August of 2018 for use with GM-CSF in patients refractory to initial therapy or with incomplete response to salvage therapy in patients older than 12 months with persistent, refractory disease limited to bone marrow with or without evidence of concurrent bone involvement (http://www.onclive.com/view/fda-approval-sought-for-naxitamab-in-neuroblastoma).

This was followed on November 25, 2020 with accelerated approval, again in combination with GM-CSF for patients older than 1 year with refractory or relapsed high-risk neuroblastoma limited to bone or bone marrow who had achieved at least stable disease to prior therapy. This approval was based on the results of two single-arm trials NCT03363373 and NCT01757626 in which patients received 3 mg/kg naxitamab IV on days 1,3 and 5 every 4-weeks in combination with SQ GM-CSF from day −4 to + 5 (250 μg/m^2/d, d – 4 to 0 and then 500 μg/m^2/d, d+1 to +5). Of 22 patients treated on NCT03363373 the objective response rate (ORR) was 45% (95% CI: 24–68%). Responses lasted 6 months or longer in 23%. Of 38 patients treated on NCT01757626, 34% had a response (95% CI: 20–50%) and 23% had responses lasting 6 months or more (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-naxitamab-high-risk-neuroblastoma-bone-or-bone-marrow). There is an international Phase 3 randomized trial (NCT04560166) in children with primary refractory disease or in first relapse with irinotecan/temozolomide ± naxitamab that is soon to open.

Pharmacokinetics and Pharmacodynamics of Anti-GD2 Monoclonal Antibodies

As previously noted, these mAbs exert their effects by both ADCC and CDC to varying degrees, depending on the specific antibody. The determinants of mAb pharmacokinetics and pharmacodynamics are dependent on multiple factors including: distribution and density of the target antigen, binding affinity to the antigen, glycosylation pattern of the antibody, immunogenicity of the mAb, rate of antibody penetration into a tumor, and effector cell number and function, among others.[83–87] Although the most effective dose is unknown, dinutuximab beta has been shown to be active at concentrations > 1 μg/mL.[26,88] Also, as previously noted, the major problem with administration of these antibodies is the induction of severe neuropathic pain, which has limited the dosage that can be given.

There are several different doses and schedules of the various anti-GD2 mAbs currently in use. Dinutuximab is given at a dose of 17.5 mg/m^2/day as a 10 to 20 hour infusion, daily x 4.[25] In an attempt to ameliorate pain, dinutuximab beta is proceeding with a 10 mg/m^2/day dose by continuous infusion x 10 days.[89] The humanized antibody naxitamab is given at 3 mg/kg day by 30-minute infusion on M-W-Fri, while hu14.18K322A is given at 40 mg/m2/day by 4-hour infusion daily x 4. Humanization has improved the tolerance, but not eliminated pain. The fact that pain resolves shortly after the mAb infusion is stopped, while the mAb still persists in the circulation suggests that pain may be related to dose-infusion rate rather that AUC.[90] A detailed review of the pharmacokinetic/pharmacodynamic parameters of these antibodies is beyond the scope of this review. Optimizing the regimen and dose to maximize tolerability and response still needs some work.

Anti-GD2 Antibody Conjugates

^{131}I-3F8

^{131}I-3F8 has demonstrated specific and sensitive imaging of metastatic NB,[91] as have three other anti-GD2 mAbs ^{131}I-14G2a,[23] 99mTc-ch14.18[92] and Cu-p-NH$_2$-Bn-DOTA -hu14.18K322A.[93] However ^{131}I-3F8 is the only one that has been used for radioimmunotherapy of patients.[94,95] The addition of ^{131}I-3F8 to a multimodality treatment for newly diagnosed children with high-risk NB did not improve their progression free or overall survival, compared to those who did not receive ^{131}I-3F8.[50,95]

Hu14.18-IL-2

Interleukin-2 (IL-2) improves the ability of effector cells to kill neuroblasts[96,97] but has significant systemic side effects.[98] The immunocytokine hu14.18-IL-2 was created to augment the antitumor effect of hu14.18 with IL-2[99] and at the same time limit the toxicity of systemic administration of IL-2.[100] In a Phase I trial hu14.18-IL-2 was given to 27 children with recurrent/refractory NB and one with melanoma, IV over 4 hours qd x 3 at various dose levels. Three patients had evidence of tumor responses.[101] In a subsequent Phase II study, patients were stratified into those with measurable disease (stratum 1; n = 13) and those with evaluable disease by bone marrow histology

and/or ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy (stratum 2; n = 23). Those with bulky disease (stratum 1) had no responses while 5/23 patients on stratum 2 had marrow CRs.[102] On the whole, adverse events were similar to those reported for other anti-GD2 mAbs when given with IL-2. Three patients discontinued treatment because of toxicity, two with acute vascular leak ± hypotension and one with a grade 4 allergic reaction.[102] Thus this hu14.18-IL-2 conjugate did not seem to significantly improve the adverse event profile of hu14.18.

Other Antibody Targets in Neuroblastoma

O-Acetyl-GD2

The O-acetyl derivative of the ganglioside GD2 is expressed on neuroblasts but not on peripheral nerves.[103] A chimeric O-acetyl anti-GD2 mAb, c.8B6, has been shown to kill neuroblastoma cells without inducing allodynia in an animal model and offers promise that it may be better tolerated than dinutuximab.[104,105] This antibody has not yet been clinically evaluated.

B7-H3 (CD276)

This is a membrane protein involved in the regulation of T and NK cells and is overexpressed on many solid tumors, including neuroblastoma.[106–108] Expression on a neuroblast cell line protected neuroblasts from NK-cell killing[106] and overexpression on tumors often correlates with faster tumor progression and poor outcome.[109] Omburtamab (8H9), a murine antibody that recognized B7-H3,[110,111] has been linked to ^{131}I (Burtomab) and used to treat children with Central Nervous System NB. In a phase 1 study, 80 patients were treated with burtomab in combination with intraventricular compartmental chemotherapy with irinotecan, temozolomide and carboplatin. Improvement on imaging was seen in 36% of children with measurable disease with a median duration of response of 49 weeks (range, 2.6 to 586 weeks).[10,112,113] Based on these data burtomab was granted Breakthrough Therapy designation for metastatic NB (https://www.cancertherapyadvisor.com/home/cancer-topics/pediatric-cancer/burtomab-granted-breakthrough-therapy-designation-for-metastatic-neuroblastoma/). A humanized anti-B7-H3 mAb, enoblituzumab, has been evaluated in a Phase I trial in children with various solid tumors, including NB [NCT02982941]. Results are not yet available.[114]

ALK (Anaplastic Lymphoma Kinase)

Mutations of ALK are observed in about 8% of all neuroblastomas[115] and small molecule tyrosine kinase inhibitors of ALK are being used clinically in these patients [NCT03126916]. The native ALK protein is expressed on the majority of NB cells and not on normal cells,[116] making treatment with an antibody targeting this protein a possibility. In human derived NB cell lines an ALK antibody inhibits growth in the absence of immune effector cells and is also able to mediate ADCC.[116] Anti-ALK antibodies are not yet available for clinical testing.

PD-1/PD-L1 (Programmed Cell Death-1; Programmed Death-Ligand 1)

PD-1 and its ligands, PD-L1 and PD-L2, are molecules involved in the regulation of the immune system and part of multiple pathways called immune checkpoint pathways.[12] Several cancers, including NB,[117] make use of these pathways to inhibit tumor cell killing by immune effector cells. In a preclinical model of NB, when treated with dinutuximab beta, PD-L1 expression on neuroblasts was upregulated. When a murine anti-PD-1 mAb was combined with dinutuximab beta a synergistic antitumor response was seen.[118] These data prompted the use of nivolumab, an antibody specific for PD-1, in combination with dinutuximab beta for the treatment of two heavily pretreated refractory patients, leading to a CR in one and VGPR in another.[119] This report suggests that immune checkpoint inhibitors combined with anti-GD2 mAbs may be a promising approach to treat NB.

GPC2 (Glycosylphosphatidylinositol Anchored Signaling Co-Receptor Glypican 2)

Glypicans are a group of cell-surface glycoproteins linked to heparan sulfate glycosaminoglycan chains and regulate a number of growth and survival functions during embryogenesis.[120] GPC2 is expressed at high levels on most NB, but not on normal tissues and is required for neuroblast cell proliferation.[121] An antibody against GPC2 conjugated to pyrrolobenzodiazepine, a DNA crosslinking agent, induced cytotoxicity, in seven human NB cell lines.[121] These data suggest that GPC2 may be

a promising new target for an anti-GPC2 mAb antibody drug conjugate.[122]

CD47

Integrin-associated protein (IAP) or CD47 is a transmembrane glycoprotein that is expressed on the surface of many types of cancer cells,[123] including NB.[124] It is an immune checkpoint on macrophages that functions as a "don't eat me" signal and has been co-opted by many types of cancer to prevent tumor cell killing.[123,125,126] Paraffin embedded tumor tissues of 66 NB patients were tested for expression of CD47 and 28/66 (42.4%) were positive, significantly more of these patients were high-risk, compared to low risk (P = 0.049).[124] Since macrophages frequently infiltrate metastatic NB tumors[127] and since CD47 is frequently expressed on high-risk tumors, the combination of dinutuximab with an anti-CD47 antibody was evaluated in pediatric xenograft models of NB and the combination was found to be synergistic.[128] This combination will soon be tested in children.[128]

Bispecific Monoclonal Antibodies (bsAbs)

Bispecific antibodies are constructed with two different antigen-binding sites[129] and for NB have been used to redirect activated T-cells to GD2 expressing neuroblast cell lines.[130] These data supported the development of a clinical trial using the humanized 3F8 anti-GD2 mAb combined with CD3 (Hu3F8-BsAb; Nivatrotamab) which is currently recruiting patients [NCT03860207]. Another bsAb, coupling an anti-GD2 antibody with a B7-H3 antibody has been developed with the goal of limiting off-target binding to GD2+/B7-H3 negative cells and reducing neuropathic pain.[131] This bsAb, INV721, binds to tumors that express both GD2 and B7H3 but minimally to cells that do not express both antigens and is capable of ADCC.[132]

Discussion

Despite intensive multimodal therapy, many children with high-risk neuroblastoma still have poor outcomes. GD2, because of its consistent expression on neuroblasts, has been targeted by several different mAbs to improve the outcome of these patients (Table 1). As previously described, the use of dinutuximab with GM-CSF, IL-2 and isotretinoin, has dramatically improved the outcome of these patients leading to the first approved immunotherapy for children with solid tumors.[25] Although these results are very promising, significant challenges remain to optimize these results for more children with this aggressive and deadly cancer. Significant toxic effects of dinutuximab included pain, hypersensitivity reactions, capillary leak and hypotension.[25] Next generation antibodies were humanized (hu14.18K322A), or fully human (naxitamab) to improve tolerability and reduce the development of neutralizing antibodies. Hu14.18K322A was further modified to reduce complement activation,[76] to ameliorate pain, an on-target, off-tumor effect of antibody binding to peripheral nerves and activating complement.[39] Although this modification appears to improve the tolerability of hu14.18K322A, when compared to dinutuximab,[78] this is not the whole answer. Is it possible that targeting the O-acetyl derivative of GD2, which is expressed on neuroblasts but not on peripheral nerves will alleviate this problem? Antibodies to this target are not yet available for clinical use. The humanization of hu14.18K322A has allowed significant dose escalation (40 mg/m^2/dose),[79] when compared to dinutuximab (17.5 mg/m^2/dose) and the fully human naxitamab is able to be administered in an outpatient setting.[82] Another structural modification to enhance ADCC is incorporated in the production of hu14.18K322A, and that is it is produced in a cell line that results in decreased fucosylation. Absence of fucose can improve antibody affinity to effector cells by up to 50-fold.[133,134]

Another augmentation to treatment with anti-GD2 mAbs has been to add cytokines such as GM-CSF[42] and interleukin-2,[135] because of their ability to enhance ADCC. Recent data have cast doubt on the added value of IL-2 because of significant added toxicities[73] and its possible role in suppression of anti-tumor immune response[136] through induction of regulatory T cells.[137] It is possible that other cytokines such as Interleukin-15[138] or IL-21[139] will further enhance the effectiveness of anti-GD2 mAbs, without the significant toxicities of IL-2.

The initial evaluation of dinutuximab focused on treatment of patients after recovery from consolidation, in a state of minimal residual disease. This is because traditionally chemotherapy has been thought to be too immunosuppressive to combine with monoclonal antibodies. However recent studies suggest, even in the setting of "bulky" solid tumors, the combination of chemotherapy

with monoclonal antibodies can be synergistic.[140–143] In other preclinical studies chemotherapy can increase the efficacy of immunotherapy by depleting immunosuppressor cells such as regulatory T-cells which are known to suppress NK cell-mediated immunotherapy,[144–146] the presumed major effector cells of anti-GD2 mAb induced ADCC in neuroblastoma.[24,147] Also chemotherapy-induced tumor cell death can trigger tumor antigen release, uptake by antigen processing cells and an enhanced anti-tumor immune response.[140,145,148] For these reasons we combined hu14.18K322A with induction chemotherapy in newly diagnosed children with high-risk NB in a single institution pilot Phase II study. All patients had clinical benefit with a near doubling of early responses, compared to a group of patients who received identical chemotherapy without hu14.18K322A, improvement in Curie Scores and no progressions during induction.[79] These results suggest that anti-GD2 mAbs can have significant activity in bulky disease if utilized with the "right" combinations. More work needs to be done to determine how best to integrate these antibodies into standard treatment. The impressive improvement in event free survival with the use of dinutuximab has provided a "proof of principle"[149] for further refining therapy using antibodies to other targets such as those described above.

Conclusion

The use of the chimeric anti-GD2 mAb following consolidation in newly diagnosed children with high-risk disease has revolutionized the treatment of these patients. The resulting improvements in EFS has led to enthusiasm that optimization of antibody design, addition of additional cytokines to further enhance ADCC and or mAbs to other targets will lead to more cures with less toxicity. Vaccines or cellular therapies such as chimeric antigen receptor (CAR) T cells[150–152] or adoptive NK cells,[153–156] although beyond the scope of this review, could further improve the treatment of these challenging patients.

Disclosure

The author reports no conflicts of interest in this work.

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