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Dinutuximab for the treatment of pediatric patients with high-risk neuroblastoma
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ABSTRACT
Neuroblastoma (NB) is the most common extra cranial solid tumor of childhood, with 60% of patients presenting with high-risk (HR) NB by means of clinical, pathological, and biological features. The 5-year survival rate for HR-NB remains below 40%, with the majority of patients suffering relapse from chemorefractory tumor. Immunotherapy is the main strategy against minimal residual disease and clinical experience has mostly focused on monoclonal antibodies (MoAb) against the glycolipid disialoganglioside GD2. Three anti-GD2 antibodies have been tested in the clinic including murine 14G2a, human-mouse chimeric ch14.18 and 3F8. Anti-GD2 MoAb induces cellular cytotoxicity against NB and is most effective when effector cells like natural killer cells, granulocytes and macrophages are amplified by cytokines. The combination of cytokines IL-2 and GM-CSF with the anti-GD2 MoAb ch14.18 (Dinutuximab) has shown a significant improvement in outcome for HR-NB. The FDA and EMA approved dinutuximab (Unituxin®) in 2015 for the treatment of patients with HR-NB who achieved at least a partial response after multimodality therapy.

Disease background
Neuroblastoma (NB) is the most common extracranial solid tumor of childhood, with 50–60% of patients presenting with high-risk (HR) NB by means of clinical, pathological, and biological features [1]. Currently, therapy for HR-NB includes induction treatment with chemotherapy and surgery, consolidation therapy with high-dose multi-agent chemotherapy rescued with autologous stem cell transplantation (ASCT) and radiation therapy, and maintenance therapy to manage minimal residual disease (MRD). Intensive induction chemotherapy and aggressive surgery have improved remission rates in young patients [2–4]; results have been modest in adolescents in whom NB is especially chemoresistant [5,6]. Despite intensive multimodal therapy, long-term survival rates for HR-NB remain at 30–40%. The complete eradication of NB is rarely achieved and the majority of patients with HR-NB suffer a relapse from chemorefractory residual tumor cells [7].

Postsurgical use of local radiotherapy helps control MRD in the primary site [8]. Myeloablative therapy with ASCT has been the most common approach for eradicating MRD in distant sites [9]. A randomized CCG study yielded improved results using total body irradiation (TBI) within the cytoreductive regimen of ASCT [10]. Due to toxicity concerns, TBI is no longer used [11–14], nonetheless ASCT has become the standard approach for MRD management in HR-NB. Extensive experience, however, has shown an uncertain benefit of ASCT for refractory NB, and recent updates of overall survival (OS) data appear to question the effectiveness of ASCT for MRD control in HR-NB patients [15–17].

Immunotherapy
Immunotherapy has been tested over the last 3 decades as a potential strategy against systemic MRD. Most of the clinical experience with immunotherapy of NB has focused on monoclonal antibodies (MoAbs) against NB cell membrane antigens including cell adhesion molecules NCAM and L1-CAM, B7-H3 glycoproteins targeted by the 8H9 MoAb and the glycolipids GD2, GD3, and GM3 [18–22]. In 1985, Cheung and colleagues described for the first time four MoAbs against, at the time, an unknown glycolipid antigen on the surface of human NB cells [23]. The murine IgG3 anti-GD2 MoAb 3F8 was initially developed by undergoing subsequent extensive preclinical testing eventually being the first anti-GD2 MoAb to be administered to patients with HR-NB [24].

GD2 is a ganglioside which are acidic glycolipids found on the outer cell membrane. They are concentrated in nervous tissues where they serve as membrane receptors for viruses and are important for cell adhesion [25,26]. GD2 is biosynthesized from precursor gangliosides GD3/GM3 by the β-1,4-N-acetyl-galactosaminyltransferase (GD2 synthase) [27] and is expressed in most NB regardless of stage, and is highly abundant, with an estimated 5–10 million molecules/cell (Figure 1) [29]. Therapeutic responses were obtained in Phase I and II studies of different anti-GD2 MoAbs such as 3F8, murine IgG2 MoAb 14G2a, and human-mouse chimeric MoAb ch14.18 [24,30–36]. Ch14.18 was constructed by combining the variable regions of original murine IgG3 anti-GD2 MoAb 14.18 and the constant regions of human IgG1 (Figure 2) [38]. In a Phase I clinical trial reported by Yu and colleagues, 10 HR-NB patients received a total of 19 courses of anti-GD2 MoAb
ch14.18 at doses of 10–200 mg/m²/course. One partial response (PR) and four mixed responses were observed in nine evaluable patients [35]. Another Phase I trial of ch14.18 by Handgretinger et al. used 30–50 mg/m²/day × 5 days/course, and two complete and two PR in nine patients were reported [39]. The biological activities of the anti-GD2 MoAb ch14.18 in vivo have been demonstrated by the capacity of post-infusion sera to mediate complement dependent cytotoxicity [35] and antibody-dependent cellular cytotoxicity (ADCC) [40,41]. Pharmacokinetic and immunological studies showed the differences between the anti-GD2 MoAbs; for instance ch14.18 has a longer plasma half-life [33,42] and less immunogenicity when compared to the murine MoAb 14G2a (Figure 2). However, toxicities of all anti-GD2 MoAbs were similar in all early studies [31,32,34,35,43]. The most common toxicities include difficult to treat pain, tachycardia, hypertension, hypotension, fever, and urticaria. Many of these toxicities are dose-dependent and are rarely noted at low dosages [35]. The pain associated with anti-GD2 therapy is similar to other neuropathic pain syndromes and is relatively opioid-resistant. Other toxicities include hypotension, nausea, vomiting, diarrhea, serum sickness, and occasional changes in pupil reaction to light and accommodation [42,43].

**Anti-GD2 immunotherapy and cytokines**

By activating ADCC to kill NB, anti-GD2 MoAbs are most efficient when effector cell populations including natural killer (NK), granulocytes, and macrophages are amplified by cytokines (Figure 3). Since NK cells and granulocytes are effectors for ADCC, the cytokines IL-2 and GM-CSF were administered in combination with anti-GD2 MoAbs to enhance their activity.

GM-CSF has been shown both in vitro and in vivo to enhance antitumor immunity through direct activation of monocytes, macrophages, dendritic cells, and ADCC [57], and indirect T-cell activation via tumor necrosis factor, interferon, and IL-1 (Figure 3) [44,46–49,57,58]. GM-CSF may enhance functions of cells critical for immune activation against tumor cells, alone or with other cytokines or MoAbs, making it an important agent in cancer biotherapy.

GM-CSF-dependent ADCC was studied in 34 patients with a variety of tumors post-ASCT including 3 with NB [50]. A significant increase in monocyte-mediated ADCC following GM-CSF therapy was documented. GM-CSF has the potential for amplifying anti-GD2 MoAb antitumor activity in patients via its effects on granulocytes and tissue-based macrophages. Granulocyte production is only transiently suppressed with chemotherapy and GM-CSF increases numbers of circulating neutrophils and eosinophils but does not affect complement levels, and is well tolerated [45]. Granulocytes from patients receiving chemotherapy and from normal volunteers are effective in mounting ADCC against NB cells via non-oxidative mechanisms, and GM-CSF enhances this cytotoxicity [44,46–50]. Eosinophilic infiltration of some cancers has favorable prognostic significance, and eosinophils exhibit potent antitumor activity in animal models. Activated monocytes-macrophages efficiently phagocytose NB cells and exposure in vitro or in vivo to GM-CSF primes monocytes-macrophages for greater antineoplastic cytotoxicity [44,46–49]. GM-CSF enhances the proliferation, maturation, and function of antigen-presenting cells. This includes antigen processing and presentation by macrophages and dendritic cells effects that might promote induction, or antitumor activity, of an idiotypic network [44,46–49].

Importantly, the addition of GM-CSF to anti-GD2 MoAbs has led to remarkable responses in patients with refractory NB [57,59,60]. The analysis of 53 patients with bone marrow (BM) disease refractory to conventional treatment showed that 85% achieved BM complete remission (CR) and 9/14 had normalization of MIBG scans after therapy with MoAb 3F8 + GM-CSF [60]. Toxicities were similar to those observed with Phase I studies of MoAb 3F8 alone. Subsequently, a Phase II trial compared the efficacy of intravenous (iv) versus subcutaneous (sc) GM-CSF in combination with MoAb 3F8 in patients with refractory NB. sc GM-CSF showed better efficacy as compared to iv administration. Retrospective review of the
experience with MoAb 3F8 plus sc GM-CSF and oral cis-retinoic acid (CRA) showed a 5-year progression-free survival (PFS) rate of 62% and OS of 81% in patients with HR-NB treated in first remission [60]. Nevertheless, a final proof of the contribution of GM-CSF has not been tested in a randomized trial.

IL-2 (Aldesleukin) causes activation of NK cells, generation of lymphokine-activated killer cells and augments ADCC (Figure 3) [41,51–56]. An early Phase II trial with IL-2 showed a modest antitumor effect as a single agent [61]. IL-2 was administered to children with refractory solid tumors and no antitumor effects were observed in children with sarcomas or NB, whereas one of five children with renal cell carcinoma had CR. IL-2 was administered post-ASCT in a variety of diseases including NB [56,62] to eradicate the residual malignant cells via immune activation. At the time, the CCG-0935 Phase I study of MoAb ch14.18 + GM-CSF [57] was amended to substitute IL-2 for GM-GSF in alternate cycles [58]. After engraftment, patients were given ch14.18 at 40 mg/m² with GM-CSF (Courses 1 and 3) or 20 mg/m² with IL-2 (Course 2). However, an increase in toxicities was observed including pain, fever, capillary leak, O₂ requirement due to capillary leak, hypotension, mild reversible increased hepatic transaminases, and infection. Subsequently, the antibody dose was changed to 25 mg/m² for both the GM-CSF and IL-2 cycles and the IL-2 dose was reduced in an attempt to decrease capillary leak. A total of 25 patients were enrolled. The MTD of MoAb ch14.18 was determined to be 25 mg/m²/day for 4 days alternated with 4.5 × 10⁶ U/m²/day of IL-2 for 4 days. IL-2 was also administered at a dose of 3 × 10⁶ U/m²/day for 4 days starting 1 week before MoAb ch14.18. Two patients experienced dose-limiting toxicity due to ch14.18 and IL-2. Common toxicities included pain, fever, nausea, emesis, diarrhea, urticaria, mild elevation of hepatic transaminases, capillary leak syndrome, and hypotension. These findings indicated that MoAb ch14.18 in combination with IL-2 was tolerable in the early post-ASCT period. It is relevant to note that overall, the reports using IL-2 for the treatment of HR-NB were feasibility and toxicity studies in the post-ASCT setting and were not designed to answer antitumor efficacy [57,58,61–64]. The most recent data challenge the use of IL-2 on the basis of a randomized trial using long-term infusion of ch14.18 combined with or without sc IL-2 for relapsed or refractory NB patients [65]. The addition of IL-2 increased pain and did not enhance anti-GD2 cytotoxicity which therefore did not support the use of IL-2 as a co-stimulatory cytokine for anti-NB purposes.

**The convincing proof of anti-GD2 immunotherapy**

Although MoAb 3F8 plus sc GM-CSF and oral CRA without IL-2 in a series of single-arm studies showed an unprecedented PFS and OS among patients with HR-NB [60], the definitive proof of efficacy for anti-GD2 immunotherapy could not be ascertained until a randomized control study was carried out. The Cooperative German Neuroblastoma trials NB90 and NB97 with the antibody ch14.18 showed initially controversial results. Antibody ch14.18 was applied as consolidation treatment in pilot patients of the NB90 and all HR patients of the NB97 trials. Early analysis did not demonstrate reduction of the event-free survival (EFS) [43]. A longer follow-up analysis, however, suggested a benefit of antibody ch14.18-based consolidation therapy compared to no consolidation therapy on EFS and OS [66]. The 9-year EFS rates were 41%, 31%, and 32% for ch14.18, NB90 maintenance chemotherapy, and no consolidation, respectively (p = 0.098). Antibody ch14.18 treatment as consolidation improved the long-term outcome compared to no additional therapy (p = 0.038) [66].

In 2010, the Children’s Oncology Group (COG) reported a randomized Phase 3 study in which 226 patients with HR-NB in remission after ASCT were randomized to receive immunotherapy or CRA alone [67]. Patients on the immunotherapy arm
received MoAb ch14.18 at 25 mg/m²/day for four consecutive days in five consecutive 4-week cycles; GM-CSF at 250 μg/m²/day for 14 days (starting 3 days before ch14.18) in cycles 1, 3, and 5; IL-2 at 3.0 × 10⁶ IU/m²/day for 4 days in week 1 and at 4.5 × 10⁶ IU/m²/day in week 2; and CRA at 160 mg/m²/day in the last 2 weeks of all six cycles. Patients in the standard chemotherapy group received CRA at 160 mg/m²/day in the last 2 weeks of all six cycles. At a median follow-up of 2.1 years, MoAb ch14.18 recipients (n = 113) had significantly higher EFS rates (66 vs. 46%; p = 0.01) and OS rates (86 vs. 75%; p = 0.02) compared with standard therapy recipients (n = 113). Since then, a Phase 3 safety trial (NCT01041638; ANBL0931) in newly diagnosed HR-NB patients who achieved at least PR to induction therapy and received consolidation with ASCT (n = 105) was conducted with maintenance treatment for all patients with MoAb ch14.18 (5 cycles) in combination with GM-CSF (cycles 1, 3, 5), IL-2 (cycles 2, 4), and CRA (6 cycles). Updates from the original data have shown a consistent 2-year EFS and OS rates of 74% and 84%, respectively [68]. However, the 4-year (from randomization) EFS rate was not anymore significant (p = 0.1) but the 4-year OS rate still remained significantly improved (p = 0.02) with immunotherapy [69].

From chimeric MoAb ch14.18 to dinutuximab (unituxin*)

In July 2010, United Therapeutics Corporation (UTC) initiated a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI), USA to collaborate on the late-stage development and commercialization of MoAb ch14.18. As such, under the CRADA, UTC had exclusive rights to the technical information required to manufacture comparable MoAb ch14.18 in the murine myeloma cell line SP2/0. Since then, UTC has developed the manufacturing process to produce MoAb ch14.18 (named dinutuximab) comparable to that from the NCI and on a commercial scale [70]. UTC has sponsored one Phase 2 study with dinutuximab in combination with GM-CSF, IL-2, and CRA for HR-NB patients, Protocol DIV-NB-201, designed to compare the pharmacokinetic profile of ch14.18 manufactured by two independent facilities; UTC and NCI. This study also compared the safety and toxicity profile of UTC-manufactured dinutuximab versus NCI-manufactured ch14.18. On 10 March 2015, the US FDA and on the 14 August 2015, the European Medicines Agency (EMA)-approved iv dinutuximab, in combination with GM-CSF, IL-2, and CRA for the treatment of pediatric patients with HR-NB who achieved at least PR with prior first-line multi agent, multimodality therapy. Dinutuximab is now Unituxin®, a registered trademark from UTC.

The recommended dosage of dinutuximab is 17.5 mg/m²/day administered iv over 10–20 h for four consecutive days for a maximum of 5 cycles. The infusion of dinutuximab is to be initiated at a rate of 0.875 mg/m²/h over 30 min and the rate can be increased gradually, as tolerated, to the maximum rate of 1.75 mg/m²/h. Unituxin® is supplied as a sterile solution in single-dose vials containing 17.5 mg/5 mL (3.5 mg/mL) in 20 mM histidine, 150 mM NaCl, 0.05% Tween 20 at pH 6.8. Dinutuximab should be diluted with 0.9% sodium chloride for injection prior to iv infusion and the required dose withdrawn from the vial and the exact volume for the 17.5 mg/m²/day dose injected into a 100 mL bag of 0.9% sodium chloride. The supplied dinutuximab does not require filtration during preparation nor does it need to be protected from light during administration. Vials should be stored in the original container tightly closed at 2–8°C. Dinutuximab is stable at room temperature for at least 24 h when diluted to a concentration between 0.044 and 0.56 mg/mL; however, the final dosage form should be prepared immediately prior to administration as there is a maximum infusion time of 20 h. The minimum infusion time is 10 h. Stability data were conducted utilizing an iv bag composed of polyvinyl chloride and bis(2-ethylhexyl) phthalate (DEHP). No data are available on the stability of dinutuximab in polypropylene syringes and polyolefin iv bags (freeflex®), within the range of 0.044–0.56 mg/mL [71].

The pharmacokinetics of ch14.18 was assessed in a Phase I trial in 10 children with NB and 1 adult with osteosarcoma [34], and a pharmacokinetic analysis of 14 children [72] participating in the pivotal Phase 3 trial [67]. A population pharmacokinetic analysis was based on a clinical study (NCT01592045) in 27 children with HR-NB who received 5 cycles of treatment with dinutuximab 17.5 mg/m²/day as an iv infusion over 10–20 h for four consecutive days every 28 days in combination with GM-CSF, IL-2, and CRA. In this study, the observed maximum plasma concentration of dinutuximab was 11.5 mcg/mL, mean volume of distribution at steady state 5.4 L, clearance 0.21 L/day (which increased with body size) with a terminal elimination half-life 10 days [73].

Expert commentary

It has taken precisely 30 years from the discovery of anti-GD2 antibodies in 1985 by Cheung and colleagues [23] to the US and EU regulatory agencies approval of dinutuximab in 2015. Although we should congratulate this extraordinary advance for a rare, orphan disease with such poor prognosis, many issues remain unresolved with several uncertainties for the future.

Dinutuximab has been approved in combination with GM-CSF, IL-2, and CRA in the context of post-ASCT. Recently, an update of the initially reported long-term OS advantage for ASCT in the randomized CCG study [15] was shown to no longer support the OS advantage for ASCT [16]. Therefore, the corrected results do not support the long-standing recommendation of ASCT as the systemic consolidative treatment for HR-NB patients. In this context, the value of immunotherapy as the sole modality for managing MRD should be revisited.

The role of each of the cytokines with which dinutuximab has been approved remains to be clarified. IL-2 has not shown antitumor activity when used as a single agent against NB and the significant toxicity associated to its use should promote reevaluation. No studies have been performed using dinutuximab and GM-CSF alone; therefore, a study of sc GM-CSF alone with dinutuximab would be of great interest. Furthermore, cytokines such as IL-15 have shown similar immune activity profiles as of IL-2 and do not cause capillary leak syndrome [74]. Future developments should include combinations of dinutuximab with selected new cytokines with a better toxicity profile to enhance ADCC.
The Phase III study showing improved 2-year EFS and reported in 2010 has been updated by the COG investigators [68,69]. The improvement in EFS appears to decline over time and the final results on OS are still pending of longer follow-up. On the other hand, improved OS of HR-NB patients experiencing multiple recurrences is currently possible if an active surveillance program to detect earlier and smaller relapses is implemented. Therefore, long-term OS may now become a better endpoint to evaluate results for HR-NB than EFS, since the equivalence between relapse and lethality may no longer hold true. In this context, the importance of anti-GD2 immunotherapy in improving OS remains to be formally definitively proven.

Last, but not least, the market price of dinutuximab in the USA was recently set at $150,000 per treatment (five cycles). This is, by all means an abusive cost for a drug that has been developed at the expense of tax-payers in academic centers in the USA. The market price is now being negotiated in Europe, country by country, but it will not be cheap. The consequences of such are multiple, including that most children worldwide will remain excluded from access to this ‘novel’ therapy. Protecting children is to make sure they readily have access to the best treatments for deadly diseases like HR-NB and it should be a priority of governments to avoid unethical prices for orphan diseases.

Five-year view

Cancer Immunotherapy has revolutionized the adult cancer field in recent years and was labeled the year discovery in 2013. Drugs targeting specific processes of the T-cell function have been developed and shown extraordinary anti-tumor effects in selected tumor types, mainly melanoma. The so-called immune checkpoint inhibitors represent the first in class type of drugs that can be developed to modify T-cell response against cancer cells. It is said that immunology has come to an age where it meets oncology and all the understanding that has been gathered over the past 30 years studying anti-GD2 immunotherapy will help in devising better and more potent agents against pediatric tumors. We have learnt that native immunotherapy is critically distinct from adoptive immunotherapy and a child’s immune system relies heavily on the innate system. The anti-GD2 MoAb experience has been the leading spear in this field which I predict will rapidly provide more potent and less toxic agents. The recent initial description of potent bivalent GD2 and CD3-bispecific antibodies to redirect T cells for enhanced anti-GD2 therapy is one such example [75].

Key issues

- Neuroblastoma is the most common extra cranial solid tumor of childhood, with 50–60% of patients presenting with HR features.
- The complete eradication of NB is rarely achieved with conventional multimodality therapy and the majority of patients with HR-NB will relapse from chemorefractory residual tumor cells.
- Anti-GD2 MoAb immunotherapy has become a clinically relevant strategy against chemorefractory MRD.
- Anti-GD2 MoAb activate ADCC to kill NB response more efficiently when effector cell populations of the innate immune system are amplified by cytokines.
- MoAb ch14.18 (Dinutuximab) is a chimeric anti-GD2 antibody produced in the murine myeloma cell line SP2/0.
- In the first trimester of 2015, the EMA and the FDA approved dinutuximab, in combination with GM-CSF, IL-2, and CRA, for the treatment of pediatric patients with HR-NB.
- Unituxin® is the registered trademark from United Therapeutics Company.

Dinutuximab is the first and only approved drug so far for the treatment of neuroblastoma.

Financial and competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:

* of interest
** of considerable interest


- In a surprisingly brief format, the COG authors of the 2009 article by the COG authors updating the results from the randomized trial of myeloablative therapy stated that the p-values were calculated in error. The consequences of this many errors have been enormous.


- A systematic review of the available data regarding myeloablative therapy for HR-NB management concluding that it appears to work in terms of event-free survival but not for overall survival.


- First historical description of anti-GD2 monoclonal antibodies produced injecting neuroblastoma into Balb/c mice and spleen cells fused to a mouse myeloma cell line SP2.


- The summary update of the MSKCC experience from 1988 to 2008 using the murine 3F8 anti-GD2 MoAb.
- The formal proof of a large randomized clinical trial showing improved outcome for patients treated with anti-GD2-based immunotherapy.