New Targeted Treatments for Cutaneous T-cell Lymphomas

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Abstract
Cutaneous T-cell lymphomas (CTCLs) represent a group of rare and heterogeneous diseases that are very difficult to treat at advanced stages. The development of monoclonal antibodies is a new hope for the treatment of these diseases. Alemtuzumab (Campath) is a humanized IgG1 kappa monoclonal antibody specific for CD52, an antigen expressed by most T and B lymphocytes. Alemtuzumab may frequently induce long-term remissions in patients with Sezary syndrome but high-dose treatments lead to severe cytopenia, immune depletion, and opportunistic infections. This treatment is less efficient in mycosis fungoides (MF). Brentuximab vedotin is a chimeric anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E, a cytotoxic antitubulin agent. Brentuximab vedotin is a very interesting new treatment for advanced tumor MF, Sezary syndrome, and primary cutaneous CD30+ lymphoproliferative disorders. The main limiting adverse event is neurosensitive peripheral neuropathy. Mogamulizumab is a humanized anti-C-C chemokine receptor Type 4 monoclonal antibody with a defucosylated Fc region leading to increased antibody-dependent cellular cytotoxicity. Mogamulizumab is very efficient on aggressive peripheral T-cell lymphomas, particularly adult T-cell leukemia/lymphoma and CTCLs, especially on the blood component of tumor cells. The main limiting events are related to the concomitant depletion of regulatory T-cells. IPH4102 is a humanized monoclonal antibody that targets the immune receptor KIR3DL2/CD158k. Preclinical results with this antibody offer proofs of concept for the clinical development of IPH4102 to treat patients with advanced CTCL.

Key Words: Alemtuzumab, brentuximab vedotin, CD158k/KIR3DL2, cutaneous T-cell lymphoma, IPH4102, mogamulizumab, mycosis fungoides, primary cutaneous CD30+ lymphoproliferative disorders, Sezary syndrome

Introduction
Cutaneous T-cell lymphomas (CTCLs) represent a group of rare, clinically and pathologically heterogeneous diseases that are very difficult to treat at advanced stages. Response to treatment is often of limited duration and especially in advanced cases, characterized by frequent recurrences, probably due to treatment resistance. It is therefore of major importance to develop new targeted immunotherapies to achieve a better treatment of these rare diseases.

Alemtuzumab (Campath; Anti-CD52 Monoclonal Antibody)
Alemtuzumab is a humanized IgG1 kappa monoclonal antibody specific for CD52, an antigen expressed by most T and B lymphocytes. For hematological malignancies, usual protocol of administration is 30 mg three times/week. Several retrospective and prospective studies have shown a good efficacy in Sezary syndrome but led to severe cytopenia, immune depletion, and opportunistic infections. To minimize immune suppression and infections, protocols of lower-dose administration have been proposed, with injection of 10 mg only if Sezary cells become higher than 1000/mm³. These protocols induce considerably less side effects but are usually not curative on a long-term perspective.

A retrospective multicenter study of alemtuzumab treatment in patients with CTCL has recently been published. This study reported the experience

What was known?
- Cutaneous T cell lymphomas are treated with skin directed or systemic therapies including retinoids like bexarotene.
- In advanced stages, histone deacetylase inhibitors, interferons or chemotherapeutic agents have been used with variable efficacy.
- The development of targeted systemic biologic therapies will benefit in the management of CTCLs.
of this treatment in 39 patients, median age 62 years (range, 20–83) treated with alemtuzumab between 2003 and 2013. Twenty-three patients had Sezary syndrome and 16 had advanced mycosis fungoides (MF). Eleven patients (28%) had transformed disease, including ten MF and one Sezary syndrome. They received alemtuzumab injections, 30 mg, 2–3 times/week, for a median duration of 12 weeks (range, 1–35). Fifteen patients received maintenance therapy for a median duration of 24 weeks (range, 6–277). After a median follow-up of 24 months (range, 0.3–124), eight patients (21%) were still alive. In this study, the overall response rate (ORR) was 51% (13 partial responses and 7 complete responses). This ORR was statistically higher in Sezary syndrome (70%) than in MF (25%) ($P = 0.009$). The median time to progression was 3.4 months (range, 0.4–42). Six patients (15%) including five Sezary syndrome and one MF remained progression free for >2 years (median, 56 months, range, 28–117). Five patients presented a cutaneous large cell transformation during treatment, and another patient developed a primary large B-cell lymphoma. Concerning adverse events (AEs), 24 patients (62%) had ≥Grade 3 infectious AE, and 10 (26%) had a hematological AE. These AEs led to treatment discontinuation in 17 patients (44%) and to death in 2 patients (5%).

These results clearly demonstrate that alemtuzumab may frequently induce long-term remission in patients with Sezary syndrome but that the results are considerably less convincing in patients with MF.

**Brentuximab Vedotin (Anti-CD30 Monoclonal Antibody)**

Brentuximab vedotin (SGN-35) is a chimeric anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E, a cytotoxic antitubulin agent. Brentuximab vedotin has shown very impressive results in the treatment of Hodgkin lymphoma, with an ORR of 75% (median, 86% and 59% complete remission (CR)).

Thirty-two patients with Stage IB–IV MF or Sezary syndrome having failed at least one prior therapy were included in a Phase 2 prospective study. They received up to 16 cycles of brentuximab vedotin (1.8 mg/kg) every 21 days. The primary end point was ORR. Thirty out of 32 included patients were evaluable. The ORR was 70% with responses in all stages. The median best modified skin-weighted assessment tool (mSWAT) score reduction was 73%. One patient presented a complete response and seven a nearly complete response (>90% reduction). The expression of CD30 by immunohistochemistry was very variable (median, 13%, range, 0%–100%). Patients with a CD30 expression lower than 5% had a decreased probability of response compared to patients with a CD30 expression higher than 5% ($P < 0.005$).

Another prospective Phase 2 study included 48 patients with primary cutaneous CD30+ lymphoproliferative disorders including lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (pc-ALCL) or CD30+ MF having failed at least one previous therapy. Response criteria for LyP were a 50% decrease in skin lesions, for pc-ALCL 50% tumor reduction and for MF 50% decrease of mSWAT. The 48 evaluable patients were 22 females and 26 males with median age of 59.5 years (range, 31–86). They included 28 with MF, 2 with pc-ALCL, 9 with only LyP, 7 LyP with MF, and 2 with pc-ALCL/LyP/MF. ORR was 71% with a complete response in 35% of cases. ORR was 50% in the 28 MF patients and 100% in LyP/pc-ALCL patients. Two pc-ALCL patients presented CRs. In these studies, the most frequent AE was peripheral neuropathy. A combined sensory-motor neuropathy occurred in 21 patients (66%) in the first trial. Twelve of these patients had a Grade 2 or higher neuropathy. The median time for the occurrence of neuropathy was 13 weeks (range, 3.0–38.6 weeks) and for Grade 2 neuropathy 20.8 weeks (range, 15.0–46.0 weeks). The median time to improvement of peripheral neuropathy was 49.0 weeks (20.4–70.1 weeks), with 59% showing improvement or resolution by 12 months and 86% by 24 months.

Other AEs were fatigue in 15 patients (41%), nausea in 9 patients (28%), alopecia, neutropenia, diarrhea, and skin eruptions. A Phase 3 trial comparing brentuximab vedotin with methotrexate or bexarotene is ongoing.

**Mogamulizumab (Anti-C-C Chemokine Receptor Type 4 Monoclonal Antibody)**

Mogamulizumab is a humanized anti-C-C chemokine receptor Type 4 (CCR4) monoclonal antibody with a defucosylated Fc region leading to increased antibody-dependent cellular cytotoxicity. CCR4 is expressed on Tregs and T-helper cells and plays an important role in skin homing. CCR4 is expressed by aggressive peripheral T-cell lymphomas (PTCLs), particularly adult T-cell leukemia/lymphoma (ATL) and CTCLs. A Phase 1/2 study was performed on 41 pretreated patients with a CTCL. Mogamulizumab was given at 0.1, 0.3, and 1.0 mg/kg once weekly for 4 weeks, followed by 1.0 mg/kg every 2 weeks. ORR was 36.8% in 38 evaluable patients, 47.1% in Sezary syndrome patients ($n = 17$), and 28.6% in MF patients ($n = 21$). Nearly 94.7% of patients with at least B1 blood involvement ($n = 19$) had a response in the blood, including eleven CRs. AEs were nausea (31%), chills (23.8%), headache (21.4%), and infusion-related reaction (21.4%).

A multicenter Phase 2 Japanese study was performed on patients with relapsed CCR4-positive PTCL ($n = 29$).
and CTCL ($n = 8$). Mogamulizumab (1.0 mg/kg) was administered intravenously once/week for 8 weeks.\textsuperscript{14} The primary end point was the ORR, and the secondary end points included safety, progression-free survival (PFS), and overall survival. On 37 evaluable patients, 13 (35%) presented an objective response, including 5 patients (14%) with complete response. The median PFS was 3.0 months. The most common AEs were lymphocytopenia (81%), neutropenia (38%), thrombocytopenia (38%), and pyrexia (30%). Almost 51% of patients presented a treatment-related skin disorder with 11% Grade 3/4 severe event. Cases of severe Stevens–Johnson-Lyell syndromes associated with mogamulizumab-induced deficiency of regulatory T-cells have been reported.\textsuperscript{15,16}

Mogamulizumab has been approved in Japan in 2012 for ATL and in 2014 for CTCL/PTCL. An international Phase 3 trial of mogamulizumab versus vorinostat in previously treated CTCL is ongoing.

**IPH4102 (Anti-CD158k Monoclonal Antibody)**

IPH 4102 is a humanized monoclonal antibody that targets the immune receptor KIR3DL2/CD158k. This receptor belongs to the family of killer cell inhibitory receptors that are expressed by natural killer cells and by a minority of CD8 lymphocytes but not by most normal CD4 T lymphocytes. CD158k is expressed by tumor T cells of Sezary syndrome, advanced MF, and pc-ALCL.\textsuperscript{17-22} CD158k acts as an inhibitory coreceptor in Sezary cells given its ability to downmodulate CD3-dependent early signaling events. In addition, our data provide evidence for a possible role of KIR3DL2 in the maintenance of a high circulating malignant-cell burden by preventing activation-induced cell death. Potent antitumor properties of IPH4102 were shown in allogeneic human CTCL cells and in a mouse model of KIR3DL2+ disease. In these models, the antitumor activity of IPH4102 was mediated by antibody-dependent cell cytotoxicity and phagocytosis. IPH4102 induced an improved survival and a reduced tumor growth in mice inoculated with KIR3DL2+ tumors. The in vivo efficacy of IPH 4102 was further evaluated in Sezary patient cells, sorted natural killer-based autologous assays, and direct spiking into Sezary patient peripheral blood mononuclear cells (PBMC). In these experiments, IPH4102 selectively and efficiently killed primary Sezary cells, including at unfavorable effector-to-target ratios characteristic of unsorted PBMC.\textsuperscript{23} Together, these results offered preclinical proof of concept for the clinical development of IPH4102 to treat patients with advanced CTCL. Preclinical studies in cynomolgus monkeys showed the lack of toxicity of this antibody in vivo. All these results led to the orphan drug designation of IPH4102 or the treatment of CTCL in the European Union in August 2014. A Phase 1 international multicentric trial will begin in October 2015.

**Conclusions**

Humanized monoclonal antibodies represent a new hope for the treatment of severe CTCLs. Several ongoing trials with brentuximab vedotin and mogamulizumab showed interesting results in these patients with limited toxicity. IPH4102 is a new anti-CD158k monoclonal antibody that represents a new possible targeted treatment in patients with advanced CTCL.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

- Alemtuzumab, brentuximab vedotin and mogamulizumab are newer options approved for treatment of CTCLs.
- Anti-CD152k monoclonal antibody presents an exciting option in preclinical studies.

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