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Current status of anti-CD30 monoclonal antibody therapy in anaplastic lymphoma and Hodgkin's lymphoma

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Until the advent of anti-CD20 antibody therapy, the mainstay of treatment in non-Hodgkin's lymphoma (NHL) was standard chemotherapy. The combination of antibodies with chemotherapy has enhanced event-free and overall survival in both diffuse large B cell NHL and follicular NHL.¹ With this example of combined chemo/ immunotherapy to enhance clinical response, it has been considered of interest to attempt a similar approach for T cell NHL and Hodgkin's lymphoma (HL).

The search for potential targets revealed CD30 as a clearly appropriate antigen. Initially identified on Reed Sternberg cells in HL and HL cell lines using an antibody Ki 1,² CD30 is now known to have a relatively restricted distribution on activated lymphocytes, HL, anaplastic large cell lymphoma (ALCL) (Table 1) and some peripheral T cell leukaemia and lymphomas³ and is found at low levels in a number of non-haemopoietic tumours. CD30 is a transmembrane glycoprotein (105-120kDa) and a member of the TNF family and although its function is not yet completely defined, stimulation of cell growth and induction of apoptosis have been noted.⁴ In order to investigate the possibility of tumour treatment with monoclonal antibodies, initial development utilized murine antibodies. Variable responses were seen in ALCL and HL lines with both cytotoxicity and enhancement of cell growth noted.⁵ Development of murine monoclonals was restricted by the potential for a human anti-mouse response and more recent clinical studies have been conducted using humanised antibodies or chimeric antibodies.

Humanised anti-CD30 (medarex)

The anti-CD30 antibody (MDX-060) is a fully human anti-CD30 antibody which induces Fc receptor mediated killing of CD30 expressing lines and limits the growth of CD30 expressing tumour cells in a murine xenograft model.⁶ In a Phase I study, the initial regimen was a weekly infusion at doses ranging from 1 to 10 mg/kg. Tolerability was very good and 17 subsequent patients were treated with the 15 mg/kg dose schedule in the extended study reported by Ansell *et al.*⁷ At the time of report, 48 patients with advanced refractory disease (40 with HL, 6 with ALCL and 2 with other CD30 positive lymphomas) had been treated with varying doses between 1 mg/kg to 15 mg/kg. The maximum tolerated dose had not been reached but 2 SAEs had occurred related to drug administration (1 elevation of liver enzymes; 1 pulmonary ARDS syndrome) but general tolerability was very good. Objective responses were seen in 6 patients including 2 with CR (1 HL; 1 ALCL) and 4 partial responses (3 HL; 1 ALCL). Stable disease was observed in 18 patients. The overall response rate was 10.7% (by cohort 14.2%, 16.6%, 17.6% at 1 mg, 5 mg and 15 mg dose levels). There was no clear cut relationship with response to soluble CD30 levels at time of starting therapy. Combinations of this human anti-CD 30 antibody have also been shown *in vitro*, using cell lines, to have enhanced cytotoxicity in the presence of cytotoxic drugs, particularly gemcitabine and etoposide.⁸ In addition, the antibody activates NF- κ B and sensitises lymphoma cell lines to bortezomib (proteasome inhibitor) induced apoptosis⁹ suggesting that antibodies of this type may be more potent in combination. There is no clinical data on combinations in humans at present.

Table 1. Characteristics of CD30 positive anaplastic lymphomas potentially amenable to anti-CD30 antibody therapy.

Features	ALK-Positive Systemic ALCL	ALK-Negative Systemic ALCL	Primary Cutaneous ALCL
T-cell phenotype*	CD4+	CD4+	CD4+
ALK protein	+	-	-
CD30	+	+	+
Clusterin	+	+	-
EMA	+	-/+	-
Cytotoxic proteins	+ (80%)	+ (50%)	+ (70%)
Median age	<30	>50	>50
Sex	M>F	M=F	M>F
5-year OS	65%-90%	30%-40%	>90%

Cytotoxic proteins: granzyme B, perforin, TIA-1 (T-cell intracytoplasmic antigen). *Occasional cases ALCL CD8+/CD4-
Abbreviations: ALK, anaplastic lymphoma kinase; EMA, epithelial membrane antigen; OS, overall survival.

Chimeric anti-CD30 (Seattle Genetics)

SGN-30 (Seattle Genetics) utilises murine variable regions and human constant regions. The product proved to be an effective inhibitor of growth in CD30 positive cell lines apparently by a predominant apoptotic mechanism rather than antibody dependent cytotoxicity.¹⁰ There was clear efficacy seen in tumour xenografts at doses of 1-4 mg/kg with a very good side-effect profile and a dose dependent delay in tumour progression. In addition, preclinical *in vitro* and *in vivo* data demonstrate marked synergy when SGN-30 is combined with chemotherapy.¹¹

Phase I development

Initial Phase I evaluation of single dose SGN-30 was in 13 patients with relapsed refractory CD 30+ disease. The MTD was not reached at the highest dose cohort tested of 15 mg/kg.¹² Two patients in this study had a partial response; 1 patient with ALCL treated at 2 mg/kg had a 50% decrease in tumour volume and another patient with HL, treated at 4 mg/kg, had a 40% decrease in tumour volume. A subsequent Phase I multi-dose study tested doses of 2-12 mg/kg given once per week for 6 doses. Patients had diagnoses of relapsed/refractory HL²¹ or relapsed refractory CD30 positive NHL (2 ALCL/1 DLBCL). A CR occurred in a cutaneous ALCL patient and disease stabilisation occurred in 5 patients. Patients tolerated multiple doses satisfactorily^{13,14} with mild to moderate adverse events and a maximum tolerated dose was not reached at the 12 mg/kg dose level.

Phase II development

The first Phase II clinical trial with SGN-30 was designed to enrol 40 relapsed/refractory HL patients and 40 ALCL patients. Data are available for 35 evaluable patients with HL. Stable disease was achieved in 9 patients (5 of 15 at 6 mg/kg and 4 of 20 at 12 mg/kg). No objective responses were seen. Of the ALCL patients, 17 patients were evaluable, 1 patient had a CR, 3 had PR (1 long lasting) and 3 stable disease. Ten patients had progressive disease. Recruitment of ALCL patients has now been completed and results from the final dataset are awaited.^{15,16}

A small study on patients with relapsed cutaneous ALCL (N=6) using dose levels of 4 mg/kg and 12 mg/kg showed 1 CR and 4 PR, with responses seen very early in those responding to therapy. In all groups, toxicity was confirmed as mild, including pedal oedema, arthralgia and insomnia. Two grade 3/4 adverse events related to SGN-30 were pruritis and an increase in the number of skin lesions.¹⁷

Current conclusions

Based on the limited clinical data available it appears that activity of anti-CD30 antibody monotherapy is greater in ALCL (both systemic and cutaneous variants) than in HL. The patients tested in clinical trials have been heavily pre-treated and most of them have a very poor overall prognosis. It is now important to optimise doses and schedules (having confirmed the low toxicity profile) and move to the use of these agents in combination studies with conventional chemotherapy in both ALCL and HL patients.

In HL there are clearly areas for clinical inno-

vation in therapeutic terms for subgroups of disease such as the elderly and it may prove possible to assess the antibodies at first relapse as a single agent prior to further chemotherapy.

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