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CLINICAL REPORT

Molecular Markers Associated with Clinical Response to Bexarotene Therapy in Cutaneous T-cell Lymphoma

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Bexarotene (Targretin®), was registered for the treatment of cutaneous T-cell lymphoma (CTCL) in 2002, and has been reported to induce a 45% overall response. Responses are mostly partial or generate a stable, skin-restricted disease. This study explored the usefulness of a novel cancer-associated gene, *NAV3* and corresponding chromosome 12 copy numbers as possible biomarkers to monitor the therapeutic response to bexarotene in 21 Finnish patients with CTCL. Six patients (29%) reached complete remission (CR) and 3 of these remained in CR for more than 24 months, 12 (57%) reached a partial response (PR, with one stable disease) and 3 were non-responders. Low-level *NAV3* deletions were detected using a fluorescence *in-situ* hybridization (FISH) assay in the lesions of 5 patients, 4 of whom were non-responders or progressed after short PR. This occurrence of *NAV3* deletions was statistically significant compared with non-progressors ($p = 0.011$, Fisher's exact test). Chromosome 12 tetraploidy was found in the lesions of two of the 3 patients with CR who remained in remission. While such tetraploidy is a feature of proliferating normal T cells, this observation may reflect a favourable anti-tumour immune response among the skin-infiltrating lymphocytes. *Key words: bexarotene; NAV3, cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome; clinical response.*

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Cutaneous T-cell lymphoma (CTCL) is a malignancy of mature T cells ($CD3^+$, $CD4^+$, $CD45RO^+$, $CD30^-$, CLA^+), primarily affecting the skin. There are 8 subtypes of CTCL (1), the most common being mycosis fungoides (MF), primary skin $CD30^+$ lymphoproliferative disease and Sézary syndrome (SS). Chromosomal instability is a typical feature of CTCL (reviewed in 2, 3). There is currently no disease-specific targeted therapy for CTCL although therapy with monoclonal antibodies targeting either CD52 (alemtuzumab), IL2R (denileukin diftitox) or CD4 molecules (zanolimumab) are used (4). The current modes of therapy either induce apoptosis of malignant cells (psoralen plus ultraviolet A (PUVA), extracorporeal photopheresis (ECP), retinoic acid) or induce cytotoxicity (monoclonal antibodies, interferon (IFN)).

During the past decade, a new group of retinoids, the rexinoids, has proven useful in treatment of CTCL. Bexarotene (Targretin®) is a retinoid-X receptor (RXR)-selective retinoid (5), and is registered in Europe for stage IIb–IVb MF. Bexarotene induces apoptosis, and inhibits proliferation (through transforming growth factor-beta (TGF-β)) of the malignant cells (5, 6). Clinically, a 45% overall response has been achieved (7–10). The responses are mostly partial or generate a stable disease, while complete responses are seen in less than 10% of patients (10). The duration of the clinical response is highly variable, with a median of 8 months (10). There is no suitable biomarker available either for the selection of patients who are likely to respond to bexarotene or for the monitoring of the therapeutic response.

In relation to an eventual molecular biomarker, we have observed previously that allelic deletion of *NAV3* (*neuronal navigator 3*, also called *POMFIL1*), a candidate cancer gene, is frequent in CTCL (11, 12). With the array-comparative genomic hybridization technique, *NAV3* deletions have been observed with a frequency of 20–30% in CTCL patients (13), while 12q deletions, not specific for *NAV3*, were reported in another CTCL patient cohort (14). *NAV3* is a spliced gene (40 exons) located in c12q21.1 and expressed in brain tissue, activated T cells, placenta, colon and certain cancer cell lines (11, 15, 16). Accumulating evidence suggests that the *NAV3* gene is a key player in various cancers. Down-regulation of *NAV3* has been found in 40% of primary neuroblastomas and in adrenocortical carcinomas (15, 17), and *NAV3* mutations have been found in melanoma and pancreatic carcinoma (18). *NAV3* belongs to the "hill" genes of genomic landscaping associated with cancer (19). We have also found *NAV3* gene copy number changes (deletions/amplifications) in some other cancer types of epithelial origin (20–21).

As a preliminary study, we undertook to explore the usefulness of chromosome 12 aberrations, especially

copy number changes of the *NAV3* gene, as biomarkers allowing the detection of chromosomally clonal malignant T cells in CTCL patients during bexarotene therapy.

PATIENTS AND METHODS

Patients and skin samples

A total of 21 consecutive patients with proven diagnosis of CTCL who were eligible for bexarotene therapy were included. Thirteen of the patients had MF stage IB–IVA (i.e. T2N0M0B0–T4N2M0B1), 4 had folliculotropic MF (T2N0M0–T3b,N0,M0), one had CD30+ MF (T3N0M0), two had Sézary syndrome and one had peripheral T-cell lymphoma, unclassified (PTCL, T3bN1M0). The decision to start bexarotene (Targretin®, Cephalon Pharma, Cephalon, Inc., Frazer, PA, USA) therapy was based solely on the responsible clinician's decision, and it was a prerequisite (according to the drug licensing) that the patient had early-stage CTCL refractory to skin-directed therapy or had received at least one standard systemic treatment modality (4) with no benefit to the disease. Thus, the patients were allowed prior therapy for their CTCL (not with bexarotene). All patients provided written informed consent for the skin biopsies obtained for this study and the study was approved by the Ethical Review Board of Helsinki and Uusimaa Hospital District (HUS; Dnro 492/E5/05).

The first skin sample was obtained from a target CTCL skin lesion prior to bexarotene therapy. During bexarotene treatment, follow-up biopsies from the same target lesion (or skin site if the lesion was healed) were obtained 4–6 weeks after the start of treatment, irrespective of the clinical response, and after 5–6 months (if treatment continued) or at the point of treatment cessation or at the point of complete clinical response, whichever came first. The skin biopsy was divided in two, one half preserved in neutral 4% formalin and processed for routine histopathological analysis and the other half also in neutral 4% formalin and processed for fluorescence *in situ* hybridization (FISH) analyses.

Bexarotene therapy

Bexarotene (Targretin®) capsules are indicated for the treatment of skin manifestations of advanced stage CTCL patients refractory to at least one systemic treatment. Bexarotene is also effective against refractory early-stage CTCL (9). It is recommended to start bexarotene at the lower dose of 150 mg/m^2/day and then titrate up to a full dose of 300 mg/m^2/day over 2–4 weeks, while monitoring the lipid values weekly (22). Since bexarotene induces hypertriglyceridaemia (and hypercholesterolaemia) and central hypothyreosis, concomitant administration of triglyceride-lowering medication and thyroxin substitution was given according to guidelines (22). Treatment with bexarotene was continued as long as the patient experienced benefit. Complete response (CR) was defined as the clinical disappearance of all skin (and lymph node if present) lesions and partial response (PR) as a 50% or more clearance of skin disease from baseline. Progression was defined as the appearance of new lesions.

FISH analyses

Dermagene Oy Ltd (Tampere, Finland) or CliniXion Oy Ltd (continuing the business activity of Dermagene) carried out the FISH analyses on coded samples for *NAV3* and chromosome 12 on nuclei isolated from the paraffin-embedded skin biopsy samples as previously described (23). Briefly, two bacterial artificial chromosome (BAC) clones specific to *NAV3* DNA (RP11-36P3 and RP11-136F16; Research Genetics Inc., Huntsville, AL, USA) and the chromosome 12 centromere probe (pA12H8; American Type Cell Culture, Manassas, VA, USA) were used and labelled with Alexa 594-5-dUTP and Alexa 488-5-dUTP (Invitrogen, Carlsbad, CA, USA), respectively. Slides with isolated nuclei were allowed to hybridize for 48 h at +37ºC. After the FISH procedure, the slides were mounted in Vectashield Mounting Medium with 4',6-diamino-2 phenylindole dihydrochloride (DAPI; Vector Laboratories, Burlingame, CA, USA).

The coded and hybridized FISH slides were analysed by two experienced persons, who were blinded to the identity of the samples, using Olympus BX61 microscope (Tokyo, Japan) equipped with a 60× oil immersion objective and a triple-band pass filter for simultaneous detection of Alexa488, Alexa594 and DAPI (Chroma Technology Corp., Brattleboro, VT, USA). Results are indicated as the percentage of *NAV3* copy number in a total of 200 counted cell nuclei. Cells with two chromosome 12 signals (diploid cells) and only one signal for *NAV3* and cells with more than two chromosome 12 signal, but with a lesser number of *NAV3* signals (e.g. three chromosome 12 centromere signals and one *NAV3* signal) were interpreted as cells with *NAV3* deletion. Cells with more *NAV3* signals than centromere 12 signals were interpreted as cells with *NAV3* amplification. A sample was considered to be *NAV3* aberrant if the percentage of interphase cells showing amplification was more than 7% or the percentage of interphase cells showing deletion was more than 4% (calculated from normal distribution of normal sample results as mean + 3× standard deviation).

Lymphocyte cultures

As a reference for proliferating T cells, peripheral blood leukocytes were isolated from two buffy coats, obtained from healthy blood donors (Finnish Red Cross Blood Service, Helsinki, Finland) and stimulated with phytohaemagglutin (10 µg/ml in RPMI with 10% foetal calf serum (FCS)). Cell aliquots were collected at 1, 2, 3 and 4 days of culture, and cytospin preparations were hybridized with chromosome 12 centromere and *NAV3* probes for FISH analyses.

Statistical analyses

For statistical analysis, SPSS statistics 17.0 software was used (IBM Corporation, NY, USA). Variables were compared using the Fisher's exact test, because the χ^2 test was not valid. All *p*-values are two-sided and exact.

RESULTS

Clinical responses

A CR was reached in 6 of 21 patients, and a remission lasting for more than 24 months was reached in 3 of these 6 patients (Table I and Fig. 1). The duration of bexarotene therapy to reach CR ranged from one to 24 months. In one patient, bexarotene was stopped due to triglyceride elevation despite maximal dosing of lipid-lowering drugs. Bexarotene maintenance therapy has now continued for more than 5 years in one patient with Sézary syndrome and has resulted in a CR.

A PR was reached in altogether 11 of 21 patients (ranging from MF IB/ T2bN0M0) to Sézary syndrome;

Table I. *Clinical outcome of patients with cutaneous T-cell lymphoma treated with bexarotene, and fluorescence in-situ hybridization assay results of* NAV3 *and chromosome 12 copy numbers in lesional skin lesions before and during the therapy*

Clinical outcome group	Number of patients: diagnosis and stage	Duration of bexarotene therapy until clinical response	Percentage of cells with polyploid chromosome 12 centromere signals	Cases with allelic *NAV3* deletion
CR and remission lasting over 24 months	3: MF IB, MF IIA and $CD30^+$ MF	1–24 months	13–32% in biopsies during bexarotene therapy (2 patients) and 2% in post-treatment biopsy	None
CR	3: two MF IB and one SzS[a]	1.5 months–3 years with low-dose maintenance in the SzS patient	0–4%	None
PR with bexarotene maintenance therapy	6: MF IB–IIA, SS and f-MF	3 months–5 years	0–7%	None
PR initially with subsequent progression	3: MF IB, MF IIA and f-MF	1–11 months	In f-MF case: 14% trisomic nuclei (3 copies of both chromosome 12 and *NAV3*) prior to treatment and 20% post-treatment	None
PR initially, but subsequent death of disease	2: MF IIB and PTCL	2–3 months	<4%	Both cases: 4% of cells with *NAV3* deletion
Stable disease	1: MF IB	Maintenance with low-dose	3%	4–8% of cells with *NAV3* deletion
No response or progression	3: MF IB, MF IIA and f-MF	3–12 months	0–3%	MF IB: 5% of cells with *NAV3* deletion in pre-treatment sample

[a]Bexarotene stopped due to triglyceride elevation in one patient.
CR: complete clinical response; PR: partial response; MF: mycosis fungoides; f-MF: folliculotropic MF, SzS: Sézary syndrome; PTCL: peripheral T-cell lymphoma.

Table I). In 6 of these, bexarotene maintenance therapy has been carried out after the initial treatment period of 3 months. In the remaining 5 patients (MF IB-IIB, folliculotropic MF and PTCL), a PR was initially reached after one to 11 months of bexarotene therapy, but CTCL progression followed thereafter. Two of these patients, one with MF stage IIB disease (T3N1M0) and another with PTCL (T3bN1M0), showed only a limited PR after 2–3 months of bexarotene, then progressed and died soon after (Table I).

In one patient with early MF, a stable disease resulted after 18 months of therapy and the patient has since continued on a low dose (75–150 mg/day; 42–84 mg/m^2 body surface area/day) bexarotene. No response or disease progression during bexarotene monotherapy was observed in 3 cases after 3–12 months of bexarotene (Table I). Two of these patients died of CTCL soon afterwards.

Thus, in summary 15 of the 21 (71%) patients responded with complete or partial improvement to the bexarotene therapy, while in five patients there was no response or the patients died of the disease in spite of a short initial PR. One patient has remained with stable disease.

Chromosomal copy number changes in relation to bexarotene therapy

We observed two types of chromosomal copy number alterations in the target skin lesions of these patients.

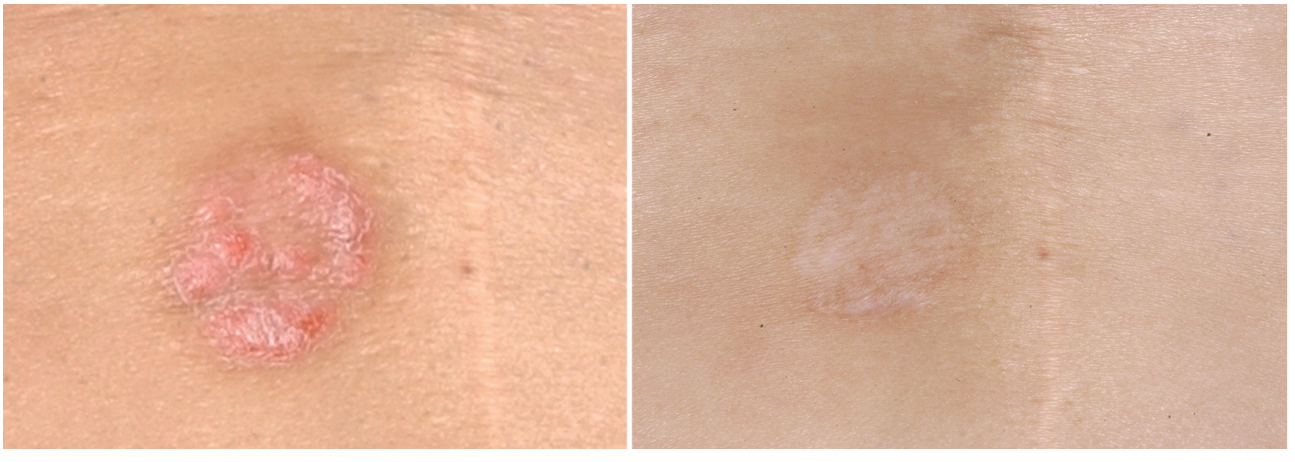

Fig. 1. Close-up of a mycosis fungoides lesion responding to bexarotene therapy. In this patient, 25–32% of the cell nuclei showed tetrasomic chromosome 12 and *NAV3* copy numbers in samples obtained during treatment.

Table II. *Summary of chromosome 12 and* NAV3 *copy number alterations in relation to bexarotene therapy response*

	Patients, *n*	Polysomy of chromosome 12 and corresponding *NAV3* amplification	Allelic *NAV3* deletion
Overall clinical response	15	3 (20%)	1 (7%)* (stable disease)
Disease progression or died of disease	6	0 (0%)	4 (67%)*

*$p = 0.011$, Fisher's exact test.

An allelic *NAV3* deletion was observed in pretreatment and follow-up samples at low frequency in five (24%) patients, 4 of whom showed an initial PR but later progressed or died of disease (Table I). The fifth patient has remained with stable (T1bN0M0B0) disease on low-dose bexarotene maintenance therapy for 2 years. The observed occurrence of NAV3 deletions in cases with clinical progression compared with stable cases was statistically significant (Table II, $p = 0.011$, Fisher's exact test).

In the group of 15 patients with a clinical response, 3 patients developed polysomy of chromosome 12 during the treatment. In contrast, this aberration was not found in any of the cases with clinical progression of disease. However, this difference did not reach statistical significance ($p = 0.526$). Tetraploidy of chromosome 12 was consistently found in the skin lesions of two of the three patients reaching CR and remaining in remission. Three copies of chromosome 12 and *NAV3*, respectively, were detected in one of the 12 patients with PR. Allelic *NAV3* amplification in association with a normal number of chromosome 12 was not found.

When normal blood donor lymphocytes were stimulated with phytohaemagglutinin (PHA), and analysed with the same FISH assay, 2–3% of the large lymphoblasts at 3 and 4 day cultures showed similar tetraploidy as in some of the patient samples (4 chromosome 12 centromere and 4 *NAV3* labels; Fig. 2). We thus conclude that the observed tetraploidy of chromosome 12 and *NAV3* in the patient samples is likely to reflect a proliferative anti-tumour response among the infiltrating lymphocytes.

DISCUSSION

The common problem with cancer therapies, even with the most recent ones, is that only a proportion of patients will respond with a clearly favourable outcome resulting in remission. There is thus an urgent need for novel biomarkers to identify patients who are likely to respond to a given therapy. Since *NAV3* is a novel cancer-associated gene (24) previously reported to show allelic deletion in CTCL (11, 12), brain tumours (25) and colorectal cancer (21), we anticipated that it might serve as a new biomarker allowing for the detection of chromosomally clonal malignant T cells in CTCL patients during bexarotene therapy and thus for monitoring the therapeutic effect of, for example, bexarotene.

Initially, a non-balanced allelic deletion of *NAV3* was observed in a substantially high proportion of CTCL patients (11). Subsequently, we and others (14) have shown (by using the current validated FISH method) that the percentage of *NAV3*-deleted cases in CTCL is in fact lower, in the order of 20%. In addition, in the current bexarotene-therapy patient material, 24% showed allelic deletion of *NAV3*, although at a low level, before and during the treatment. The patients with *NAV3* deletion mostly belonged to the group of non-responders or to those with progressive disease after a partial early response. In contrast, the appearance of cell clones with tetraploid signals for *NAV3* and for the corresponding chromosome 12 during the first few months of bexarotene therapy seemed to be associated with the most favourable clinical response, longstanding

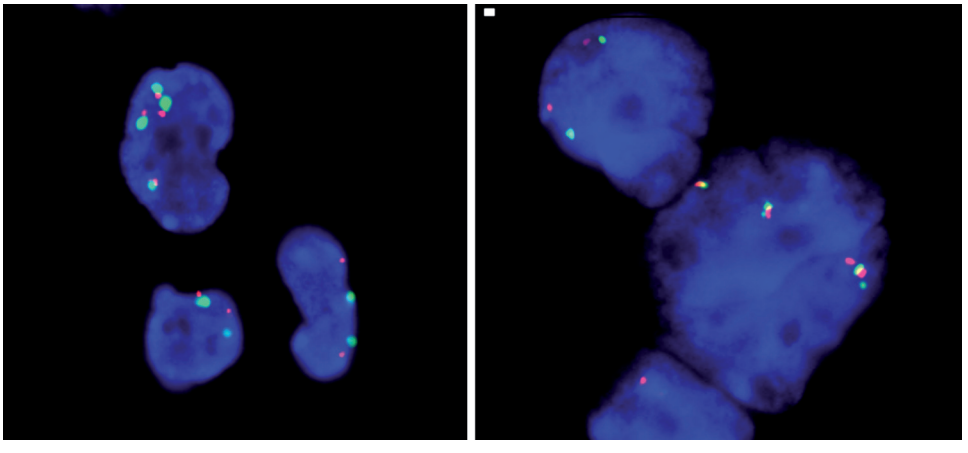

Fig. 2. Example of NAV3 (red signal) and chromosome 12 (green signal) fluorescence *in-situ* hybridization (FISH) on PHA-stimulated normal human lymphocytes showing 4 signals of both chromosome 12 and *NAV3* in some nuclei. Right-hand panel: cell in the initiating phase of cell division.

remission, in this small patient material. An indication that the tetraploid cells observed in the patient samples could represent a proliferating normal T-cell population is the fact that similar large lymphoblastoid cells with four copies of chromosome 12 were also observed in the normal lymphocytes, stimulated for a proliferative response with the PHA mitogen.

CTCL lesions are characterized by a low number of truly malignant cells and a larger population of reactive T-cells that have been proposed to exert a cytotoxic immune response towards the malignant cells (26–28). Also, as shown by recent proteome-based studies, seroreactivity against lymphoma cells can be found in CTCL patients, although these responses are restricted to few antigens and are heterogeneous in nature (29). Thus, our observation of chromosome 12 tetraploidy in the skin lesions of two of three patients with CR and remaining in remission, and polyploidy in one of 12 patients with PR, could be considered as a marker of the proliferation of either regulatory or cytotoxic T cells directed against the malignant lymphocytes.

On the other hand, the observed low-level *NAV3* deletion in 5 patients, 4 of whom did not respond to therapy, or who showed only an initial PR, and progressed or died of disease, would indicate that the consequences of the *NAV3* deletion may have an effect not only on the cancer cells as such, but also on the immune response targeted against the cancer cells. The predicted function of NAV3 indicates that it might act as a transcription factor, and recent evidence identifies NAV3 as a member of the human Navigator proteins, which function as microtubule plus-end tracking proteins (+TIPs), which in turn are involved in many cellular processes, including mitosis, and cell migration (30). We have recently shown that silencing *NAV3* induces the expression of, for example, IL23R, a key membrane molecule in inflammatory responses and associated with the JAK/STAT signalling pathway (http://www.ncri.org.uk/ncriconference: LB15). The activation of the IL23/IL23R-dependent JAK/STAT pathways may lead to the emergence of Treg cells that would inhibit the possible anti-cancer immune response (30). An abnormal IL-23 expression has been suggested to play a role in the pathogenesis and progression of MF/SS (31). Interestingly, retinoic acid has been shown to inhibit the expression of IL-23R (as well as IL-6Ralpha and IRF-4) and consequently, also Th17 development (32–33). Thus, further prospective studies on this pathway axis would be warranted in connection of bexarotene therapy. The results of this study, although a limited number of patients were involved, are in line with our earlier studies on the clinical consequences of *NAV3* copy number changes. Although the exact molecular and cellular mechanism behind the observed tetrasomy of chromosome 12 and bexarotene therapy is unknown, the indication of a favourable clinical response in such cases, especially in comparison with a clearly less favourable outcome in patients harbouring *NAV3* deletions, warrants further prospective and more detailed studies on these potential new biomarkers.

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The authors declare no conflicts of interest.

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