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(57) Abrégé/Abstract:
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IMPROVED TREATMENT OF CANCER BY DOUBLE-STRANDED RNA

The present invention relates generally to the fields of genetics and medicine. More specifically, the present invention relates to improved methods of treating cancers using double-stranded RNA compounds.

INTRODUCTION

Double-stranded RNA molecules, such as poly A-polyU and poly I-poly U, are immunostimulating agents. Preclinical studies performed in 1970-1980's showed that the incubation of blood mononuclear cells with poly A-poly U induces interferon alpha secretion, and that the injection of poly A-poly U activates natural killer cells in vitro (EP281 380 ; EP 113 162). Recently, an American team showed that the double-stranded RNA receptor is Toll Like receptor 3 (TLR3). This receptor has been described to be expressed in membranes of dendritic cells and of cells from colic mucosa. The binding of double-stranded RNA to this receptor activates dendritic cells and activates T lymphocytes.

Consequently, the use of double-stranded RNA for treating cancer has been developped. However, the response rate is not always high. Indeed, in the phase I/II poly A-poly U trial, results suggested an approximately 20% complete response rate.

Therefore, a method allowing to select responding patient would greatly enhance the therapeutic efficacy of double-stranded therapies.

SUMMARY OF THE INVENTION

The present invention demonstrates the existence of a correlation between the expression of a TLR in tumor cells in a subject and the ability of said subject to respond to treatment with a composition comprising a double-stranded RNA. More specifically, the present invention shows, for the first time, that TLR is expressed in tumoral cell membranes and that the

binding of double-stranded RNAs on said tumoral cells through the TLR leads to tumoral cells lysis and tumor regression. In contrast, tumoral cells that do not express TLR are not sensible to the double-stranded RNA treatment.

Therefore, the present invention concerns the use of a double-stranded RNA molecule for the manufacture of a medicament for treating cancer in a subject, wherein said cancer in said subject comprises cancer cells expressing a TLR3 receptor. More particularly, the present invention concerns the use of a double-stranded polyA/polyU RNA molecule for the manufacture of a medicament for treating breast cancer in a subject, wherein said breast cancer in said subject comprises cancer cells expressing a TLR3 receptor.

The present invention also concerns a method for assessing the response of a subject having cancer to a treatment using a double-stranded RNA molecule, the method comprising determining whether cancer cells in said subject express a TLR3 receptor, the expression of a TLR3 receptor being indicative of a responder subject.

The present invention further concerns a method for selecting subjects having a cancer that respond to a treatment using a double-stranded RNA molecule, the method comprising determining whether cancer cells in said subject express a TLR3 receptor, the expression of a TLR3 receptor being indicative of a responder subject.

In addition, the present invention concerns a method for treating a subject having a cancer, the method comprising determining whether cancer cells in said subject express a TLR3 receptor, the expression of a TLR3 receptor being indicative of a subject responding to a double-stranded RNA molecule, and treating said subject whose cancer cells express a TLR3 receptor with a double-stranded RNA molecule.

In a preferred embodiment of the methods and uses according to the present invention, the subject is a human subject.

In a preferred embodiment of the methods and uses according to the present invention, the cancer is a solid tumor or a carcinoma. Preferably, the solid tumor is selected from breast

cancer, colon cancer, lung cancer, prostate cancer, renal cancer, metastatic or invasive malignant melanoma, brain tumor, ladder cancer and liver cancer. Carcinoma includes bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid or skin carcinoma, including squamous cell carcinoma. However, the present invention also contemplates hematopoïetic tumors such as leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, Burketts lymphoma, acute and chronic myelogenous leukemias and promyelocytic leukemia. The present invention is also relevant for the treatment of metastasis.

In a preferred embodiment, the expression of a TLR3 receptor in said cancer cell is determined using a TLR3-specific ligand. Preferably, the ligand is an antibody, or a fragment or derivative thereof.

In an alternative embodiment, the expression of a TLR3 receptor in said cancer cell is determined using a TLR3-specific primer or probe.

Preferably, the expression of a TLR3 receptor in said cancer cell is determined in vitro or ex vivo. However, the determination in vivo is also encompassed by the present invention.

In a preferred embodiment of the methods and uses according to the present invention, the double-stranded RNA molecule is a polyA/polyU molecule. In an other preferred embodiment of the methods and uses according to the present invention, the double-stranded RNA molecule is a polyI/polyC molecule.

The present invention further concerns a kit for selecting subjects that respond to a treatment using a double-stranded RNA molecule, the kit comprising reagents for determining the expression of a TLR3 receptor in a cancer cell in a sample.

DESCRIPTION OF THE FIGURES

Figure 1 illustrates the TLR3 expression by primary tumor. TLR3 is overexpressed by TUMOR CELLS in 10% of samples (n=18)

Figure 2 illustrates Survival of patients with TLR3- tumors (figure 2a) or with TLR3+ tumors (figure 2b) according to treatment with a placebo (observation) or with dsRNA.

DETAILED DESCRIPTION OF THE INVENTION

TLR3

Toll Like Receptor 3 (NP 003256) is a member of the Toll-like receptor (TLR) family which plays a fundamental role in pathogen recognition and activation of innate immunity. TLRs are highly conserved from Drosophila to humans and share structural and functional similarities. They recognize pathogen-associated molecular patterns (PAMPs) that are expressed on infectious agents, and mediate the production of cytokines necessary for the development of effective immunity. The various TLRs exhibit different patterns of expression. This receptor is most abundantly expressed in placenta and pancreas, and is restricted to the dendritic subpopulation of the leukocytes. It recognizes dsRNA associated with viral infection, and induces the activation of NF-kappaB and the production of type I interferons. It may thus play a role in host defense against viruses. TLR3 mRNA sequence is described in NCBI accession number NM 003265. TLR3 is described in WO 98/50547.

As used in the present application, the term "TLR3 gene" designates the Toll Like Receptor 3 gene, as well as variants, analogs and fragments thereof, including alleles thereof (e.g., germline mutations). Such variants include, for instance, naturally-occurring variants due to allelic variations between individuals (e.g., polymorphisms), alternative splicing forms, etc. Variants are preferably substantially homologous to NM 003265 sequence, i.e., exhibit a nucleotide sequence identity of at least about 65%, typically at least about 75%, preferably at least about 85%, more preferably at least about 95% with NM 003265 sequence. A particular example of a TLR3 gene comprises NM 003265 sequence.Variants and analogs of a TLR3 gene also include nucleic acid sequences, which hybridize to a sequence as

defined above (or a complementary strand thereof) under stringent hybridization conditions.

Typical stringent hybridisation conditions include temperatures above 30° C, preferably above 35°C, more preferably in excess of 42°C, and/or salinity of less than about 500 mM, preferably less than 200 mM. Hybridization conditions may be adjusted by the skilled person by modifying the temperature, salinity and/or the concentration of other reagents such as SDS, SSC, etc.

A fragment of a TLR3 gene designates any portion of at least about 8 consecutive nucleotides of a sequence as disclosed above, preferably at least about 15, more preferably at least about 20 nucleotides, further preferably of at least 30 nucleotides. Fragments include all possible nucleotide lengths between 8 and 100 nucleotides, preferably between 15 and 100, more preferably between 20 and 100.

The term "gene" shall be construed to include any type of coding nucleic acid, including genomic DNA (gDNA), complementary DNA (cDNA), synthetic or semi-synthetic DNA, as well as any form of corresponding RNA. The term gene particularly includes recombinant nucleic acids encoding TLR3, i.e., any non naturally occurring nucleic acid molecule created artificially, e.g., by assembling, cutting, ligating or amplifying sequences. A TLR3 gene is typically double-stranded, although other forms may be contemplated, such as single-stranded. TLR3 genes may be obtained from various sources and according to various techniques known in the art, such as by screening DNA libraries or by amplification from various natural sources. Recombinant nucleic acids may be prepared by conventional techniques, including chemical synthesis, genetic engineering, enzymatic techniques, or a combination thereof.

A TLR3 polypeptide designates any protein or polypeptide encoded by a TLR3 gene as disclosed above. The term "polypeptide" refers to any molecule comprising a stretch of amino acids. This term includes molecules of various lengths, such as peptides and

proteins. The polypeptide may be modified, such as by glycosylations and/or acetylations and/or chemical reaction or coupling, and may contain one or several non-natural or synthetic amino acids. A specific example of a TLR3 polypeptide comprises all or part of NP 003256 sequence.

Preferably, the step of determining whether cancer cells in said subject express a TLR3 receptor is performed on a tumoral sample derived from a patient. For example, the sample can be a biopsy of the patient's tumor, a cell or tissue culture, etc. Such sample can be obtained by conventional methods. In a particular embodiment, the sample is obtained by non-invasive methods and/or from tissue collections.

Therefore, in one embodiment of the methods and uses according to the present invention, the step of determining whether cancer cells in said subject express a TLR3 receptor comprises : providing a tumoral sample from the patient and detecting the expression of a TLR3. The expression of a TLR3 may be detected at the nucleic acid level or at the polypeptide level.

Various techniques known in the art may be used to detect or quantify LTR3, including sequencing, hybridisation, amplification and/or binding to specific ligands (such as antibodies). Suitable methods include Southern blot (for DNAs), Northern blot (for RNAs), fluorescent in situ hybridization (FISH), gel migration, ELISA, radio-immunoassays (RIA) and immuno-enzymatic assays (IEMA).

Some of these approaches are particularly suited for assessing a polypeptide sequence or expression level, such as Northern blot, ELISA and RIA. These latter require the use of a ligand specific for the polypeptide, more preferably of a specific antibody.

Different types of ligands may be used, such as specific antibodies. In a specific embodiment, the sample is contacted with an antibody specific for a LTR3 polypeptide and the formation of an immune complex is determined. Various methods for detecting an

immune complex can be used, such as ELISA, radioimmunoassays (RIA) and immuno-enzymatic assays (IEMA).

Within the context of this invention, an antibody designates a polyclonal antibody, a monoclonal antibody, as well as fragments or derivatives thereof having substantially the same antigen specificity. Fragments include Fab, Fab'2, CDR regions, etc. Derivatives include single-chain antibodies, humanized antibodies, poly-functional antibodies, etc. LTR3-specific antibodies suitable for use in the present invention are commercially available, such as (TLR3 monoclonal antibodies, Ref 12-9039 and 12-9039, eBioscience, USA; or polyclonal anti TLR3, Ref ab13555, abcam, UK; etc.

In a specific embodiment, the method comprises contacting a sample from the subject with (a support coated with) an antibody specific for TLR3 polypeptide, and determining the presence of an immune complex.

In an alternative embodiment, the expression of a TLR3 receptor in said cancer cell is determined using a TLR3-specific primer or probe. Such primer or probes are designed to specifically hybridise with a TLR3 gene, under suitable hybridisation conditions, thereby allowing detection of a gene or RNA coding for TLR3. A particular embodiment comprises contacting a tumor sample from the patient with a TLR3-specific primer or probe, and determining the existence of a hybrid or amplification product. The presence (or amount) of TLR3 mRNA in a sample can provide an indication as to the expression of said receptor. Such determination may be accomplished by various techniques known in the art, including through RT-PCR. To that purpose, total RNA is isolated from cancer cells using commercially available kits, such as the RNeasy Mini kit (Qiagen, Valencia, CA). DNase I-treated total RNA (3 μg) is reverse-transcribed by using random primers with RNaseH-free reverse transcriptase (Invitrogen, San Diego, CA). TLR3 can be amplified using specific primers described below. TLR3 (5'-CTCAGAAGATTACCAGCCGCC-3'/5'-CCATTATGAGACAGATCTAATG-3') (see US2003/0165479).

Prior to determining expression of TLR3, the sample may be treated to improve availability of TLR3 nucleic acids or polypeptides. Such treatment may include, for instance, a lysis of the cells or tissue (e.g., mechanical, enzymatic or physical).

The invention also relates to a diagnostic kit comprising products and reagents for detecting in a tumoral sample from a subject the expression of a TLR3 gene or polypeptide. Said diagnostic kit according to the present invention comprises any primer, any pair of primers, any nucleic acid probe and/or any ligand, preferably antibody, described in the present invention. Said diagnostic kit according to the present invention can further comprise reagents and/or protocols for performing a hybridization, amplification or antigen-antibody immune reaction.

Double-strand RNA

Within the context of the present invention, the term "double-stranded RNA" molecule designates any therapeutically effective (synthetic) double-stranded RNA compound. Such compounds are typically active per se, i.e., they do not encode a polypeptide or do not require translation to be active. Each strand of these dsRNAs can have a length comprised between about 5 and 50 bases, more preferably between 5 and 40, 35, 30, 25 or 20 bases. Each strand is preferably perfectly complementary to the other. Preferred examples of such dsRNAs are homopolyRNAs, i.e., dsRNAs in which each strand comprises essentially a repeat of the same base ; or comprise a homopolyRNA region. The base may be any naturally occurring base (e.g., polyA, polyU, polyC, polyG) or non naturally occurring (e.g., chemically synthesized or modified) base (e.g., polyI).

Specific examples of double-stranded RNA according to the present invention include Polyadenur (Ipsen) and Ampligen (Hemispherx). Polyadenur is a polyA/U RNA molecule, i.e., contains a polyA strand and a polyU strand. Polyadenur has been developed for the potential treatment of hepatitis B virus (HBV) infection. Ampligen is of a polyI/polyC compound (or a variant thereof comprising a polyI/polyC12U RNA molecule). Ampligen is

disclosed for instance in EP 281 380 or EP 113 162. Ampligen has been proposed for the treatment of cancer, viral infections and immune disorders. It was developed primarily for the potential treatment of myalgic encephalomyelitis (ME, or chronic fatigue syndrome/chronic fatigue immune dysfunction syndrome, CFS/CFIDS).

A particular example of a dsRNA for use in the present invention is a dsRNA comprising a polyA/polyU region, wherein each strand of said dsRNA contains less than 25 bases.

An other particular example of a dsRNA for use in the present invention is a dsRNA comprising a polyI/polyC(U) region, wherein each strand of said dsRNA contains less than 25 bases.

Further dsRNAs have been disclosed in the literature or may be developed, which can be used within the present invention. More generally, any synthetic double-stranded homopolyRNA may be used in the context of this invention.

The treatment with a dsRNA molecule may be accomplished as disclosed in the literature cited above. Furthermore, the treatment may be performed either alone or in combination with other drugs or treatments. The treatment may include a reduction in tumor size, a reduction or delay in tumor growth, development or metastasis, or a regression of cancer.

Further aspects and advantages of this invention will be disclosed in the following examples, which should be regarded as illustrative and not limiting the scope of this invention.

EXAMPLES

Toll like receptor 3 (TLR3) is known to be expressed by myeloid dendritic cells (DC) and to induce their maturation following binding with double stranded RNA (dsRNA) or its synthetic homologues polyAU and polyI:C. Several clinical trials have reported that injection of dsRNA is associated with survival benefit in cancer patients. In the present

study, the inventors have asked whether dsRNA could act directly on tumor cells through TLR3. Patients and methods : 300 patients with early breast cancer have been included from 1972 to 1979 in a randomized trial comparing post-operative administration of polyAU with no treatment. Results have been reported that showed a trend for a survival benefit in patients with involved axillary lymph nodes (n=200).

Tumor biopsies from these patients were stained with TLR3-specific mAb and correlation between TLR3 expression and polyAU efficacy was determined.

To investigate directly the effects of dsRNA, both freshly isolated breast tumor cells and cancer cell lines were cultured with polyI:C, and apoptosis was measured. The involvement of TLR3 in cell response was established by TLR3 RNA interference.

Results : 182 tumor samples (91%) were available from the 200 pTxN+M0 patients included in this randomized trial. TLR3 was strongly expressed by tumor cells in 18 patients (10%). Table 1 reports the 20-year survival rates according to treatment and TLR3 expression.

Targeting Toll like receptor 3 in breast cancer : results of randomized trial and in vitro studies

<u>Material and methods:</u>

Patients:

200 patients were included in the present study. All patients had been previously included in a prospective randomized trial that compared double stranded RNA (polyAU) to placebo. This trial have already been reported elsewhere. Briefly, this randomized trial included patients with T1-3N0-3M0 breast cancer treated with surgery. Treatment consisted in weekly iv injection of polyAU (Beaufour Ipsen). A total of 6 injections were performed. PolyAU was administered at a fixed dose of 60 mg/injection. This trial initially included 300 patients. Since initial results of the trial reported a trend for benefit only in patients

with axillary lymph node involvement, only the 200 patients with axillary node involvement were included in the present study.

Immunostainings:

Tumor blocks were available in 182 out of 200 patients included in the present study. Paraffin-embedded, 5 um-thick tissue section from all 182 tumors were stained with either polyclonal antiTLR3 (gift from Dr Pobolsky, Massachusetts General Hospital, Boston) or rabbit preimmun serum. A mouse monoclonal anti-rabbit IgG was used as secondary antibody. Immunostainings were assessed by 2 pathologists who were blinded for clinical files. The TLR3 expression was classified according to the percentage of tumor cells stained and the intensity of staining. A tumor was classified as positive when more than 10% of tumor cells were strongly stained with the anti-TLR3 antibody.

Statistics:

Survival curves were determined according to Kaplan-Meier method. Survival curves were compared using Khi2 test.

Results:

Patients characteristics

One hundred eighty two tumors were processed. The immunostaining could not be interpreted in 7 patients (absence of tumor cells in 4 patients, artefact in 3 patients). The analysis was therefore performed on 175 patients. This represents 87% of the patients included in the randomized trial. The median follow-up of living patients was 23 years (12 to 26 years). The patients characteristics are reported in Table 1. Briefly, the median age is 50, the median number number of lymph node involved was 4 (1-31), 26% of tumor were staged pT3 and 35% were classified as grade III according to Scarf and Bloom Richardson.

Table 1: Patients characteristics

	TLR3- tumors (n=157)	**TLR3+ tumors (n=18)**	

Characteristics	Observation (n=77)	Poly AU (n=80)	Observation (n=10)	Poly AU (n=8)	Total (n=175)
Age (median)	50	50	52	49	50
Nb lymph node involved (median)	5 (1-31)	4 (1-27)	2 (1-8)	4 (1-9)	4 (1-31)
pT					
pT1	8	1	0	0	9
pT2	56	54	6	6	122
pT3	13	27	4	2	46
Tumor grade					
I	11	9	1	2	23
II	34	49	6	3	92
III	32	24	3	3	62
Post-operative radiotherapy					
Yes	74	77	9	8	168
No	3	3	1	0	7

Immunostainings

TLR3 was strongly expressed by tumor cells in 18 samples (10.4% of assessable tumors). Immunostainings are shown in Figure 1. TLR3 was mainly expressed on the cell surface and cytoplasm of tumor cells. In situ carcinoma and normal breast tissues were stained by anti-TLR3 in most cases. The patients characteristics of the TLR3+ tumors did not differ to that of TLR3- tumors (Table 1).

Correlation between TLR3 expression and survival after treatment with polyAU

The 20 year OS of patients treated or not with polyAU were 42% and 35% respectively (p=0.09). When only patients with TLR3- tumors were considered, the 20 year OS were 41% for patients treated with polyAU, and 37% for those assigned to observation arm

(p=0.52) (Figure 2a). When only patients presenting TLR3+ tumors were considered, the 20 year OS were 88% for patients treated with polyAU, and 22% for patients assigned to the observation arm (p=0.01) (Figure 2b).

Conclusion:

A. TLR3 is overexpressed by tumor cells in around 10% of cancer cases

B. TLR3 expression correlates with the benefit of adjuvant therapy with polyAU in patients with lymph node positive breast cancer

WHAT IS CLAIMED

1. The use of a double-stranded RNA molecule for the manufacture of a medicament for treating cancer in a subject, wherein said cancer in said subject comprises cancer cells expressing a TLR3 receptor.

2. A method for assessing the response of a subject having cancer to a treatment using a double-stranded RNA molecule, the method comprising determining whether cancer cells in said subject express a TLR3 receptor, the expression of a TLR3 receptor being indicative of a responder subject.

3. A method for selecting subjects having a cancer that respond to a treatment using a double-stranded RNA molecule, the method comprising determining whether cancer cells in said subject express a TLR3 receptor, the expression of a TLR3 receptor being indicative of a responder subject.

4. A method for treating a subject having a cancer, the method comprising determining whether cancer cells in said subject express a TLR3 receptor, the expression of a TLR3 receptor being indicative of a subject responding to a double-stranded RNA molecule, and treating said subject whose cancer cells express a TLR3 receptor with a double-stranded RNA molecule.

5. The use or method of any one of the preceding claims, wherein the subject is a human subject.

6. The use or method of any one of the preceding claims, wherein the cancer is a solid tumor and carcinoma.

7. The use or method of claim 6, wherein the solid tumor is selected from breast cancer, colon cancer, lung cancer, renal cancer, metastatic or invasive malignant melanoma, prostate cancer, brain tumor, ladder cancer and liver cancer.

8. The use or method of any one of the preceding claims, wherein the expression of a TLR3 receptor in said cancer cell is determined using a TLR3-specific ligand.

9. The use or method of claim 8, wherein the ligand is an antibody, or a fragment or derivative thereof.

10. The use or method of any one of claims 1 to 7, wherein the expression of a TLR3 receptor in said cancer cell is determined using a TLR3-specific primer or probe.

11. The use or method of any one of the preceding claims, wherein the expression of a TLR3 receptor in said cancer cell is determined in vitro or ex vivo.

12. The use or method of any one of the preceding claims, wherein the double-stranded RNA molecule is a polyA/polyU molecule.

13. The use or method of any one of claims 1 to 11, wherein the double-stranded RNA molecule is a polyI/polyC molecule.

14. The use of a double-stranded polyA/polyU RNA molecule for the manufacture of a medicament for treating breast cancer in a subject, wherein said breast cancer in said subject comprises cancer cells expressing a TLR3 receptor.

15. A kit for selecting subjects that respond to a treatment using a double-stranded RNA molecule, the kit comprising reagents for determining the expression of a TLR3 receptor in a cancer cell in a sample.

Figure 1

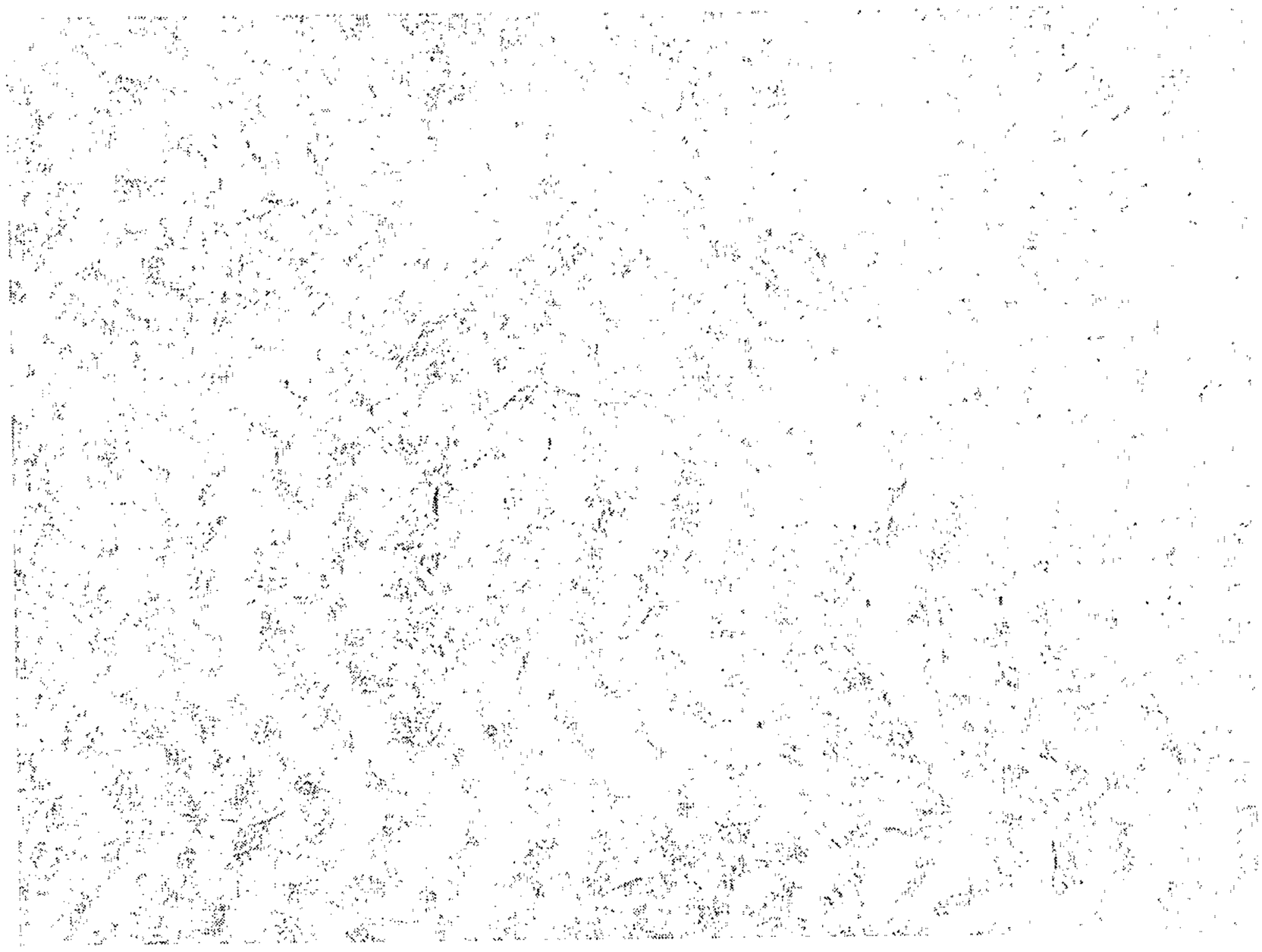

Figure 2a: Survival of patients with TLR3- tumors according to treatment

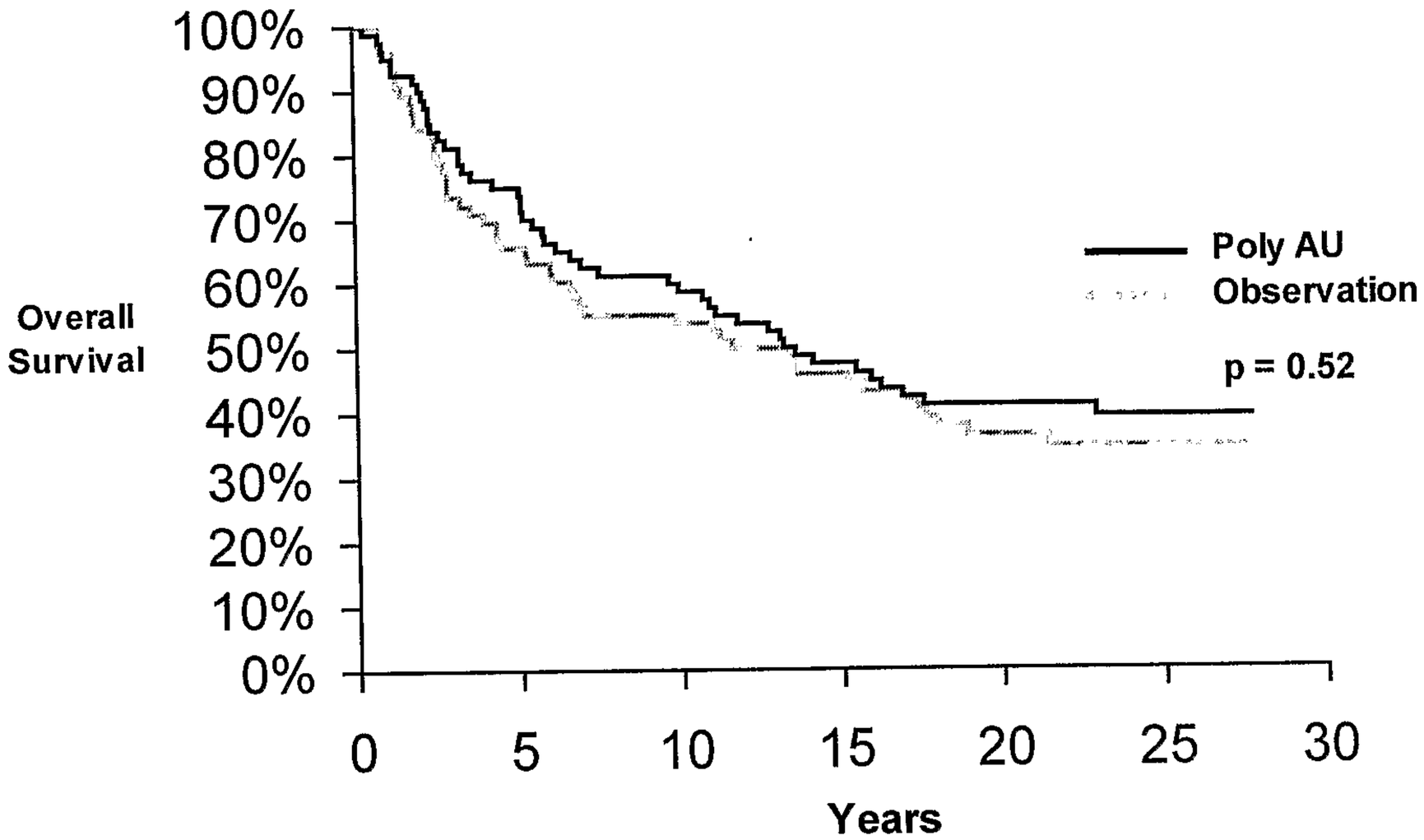

Figure 2b: Survival of patients with TLR3+ tumors according to treatment