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A SUMMARY REVIEW

Second Edition

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INTRODUCTION

ISCADOR is the trade name of a mistletoe (Viscum album L.) preparation developed and produced by the Society for Cancer Research, Arlesheim, Switzerland; and it is marketed in various countries by Weleda AG (headquartered in Arlesheim, Switzerland).

ISCADOR was introduced in the treatment of human cancer as early as 1921 when preclinical studies, especially toxicology studies, did not play as important a role as they do today in the development of a drug. At the very beginning of its development, ISCADOR was used in man, so its safety and effectiveness were directly assessed without prior evaluation in animals.

Later, when university institutes and other research institutes became interested in ISCADOR, they initiated preclinical and clinical studies, not to evaluate possible safety risks (this aspect was already covered by the clinical experiences), but to investigate its mode of action and to verify its activity in animals under standardized conditions, as well as in man under controlled clinical conditions.

In addition to its specific history, the drug itself differs in many aspects from other new anticancer drugs. ISCADOR is a complex plant extract which cannot be completely identified, and experimental studies which presume a chemically well-defined single substance cannot be conducted with it.

As a consequence, a different emphasis was made in studies to develop ISCADOR and to verify its usefulness as an anticancer drug than is usual for a new chemically defined substance. Nevertheless, the documentation supplies substantial and coherent data so that the professional reader can appraise the drug's usefulness in the treatment of cancer.

Almost all data were obtained by independent extramural investigators without any contractual relationship with the company marketing ISCADOR. Most of the scientific

References*

studies are published and consequently their results are not confidential. The independence and the scientific qualifications of the investigators are adequate assurance of the correctness and the validity of the data presented here.

*CODE REFERENCES ON THE LEFT

References on the left side of each page indicate the original document in the master file. Under chapter V. of this summary the complete references are listed by code.

OVERVIEW OF THIS DOCUMENTATION

1. RATIONALE

In comparison to the commonly used antineoplastic drugs, ISCADOR represents a different approach to the treatment of solid cancer.

The concept of ISCADOR as an anticancer drug is not only focused on the cellular aspects of the disease cancer, but based on a much broader view of the disease. The cause of the disease is seen as a deficiency of the form-giving dynamic forces of the organism, resulting in a loss of the cell's normal control of its overall growth potential. Consequently the cell's further growth and differentiation is not under the control of the organism. The development of this deficiency is fostered by the often specific reactive conditions and responsiveness of the patient which can be defined as anergic or hypoergic. This comprehensive and systemic aspect of the disease was first described by Rudolf Steiner in 1920. Based on this concept of the disease he recommended for its treatment preparations of the plant Viscum album (mistletoe) to induce a process contrary to the disease in the patient.

This documentation on ISCADOR dealswith studies to verify the usefulness of this drug in the therapy of solid cancer.

2. DESCRIPTION OF ISCADOR

ISCADOR is a whole plant extract of mistletoe and as such cannot be described completely in all its chemical complexity. The identity of ISCADOR, however, is established by thin layer chromatography. The degree of cytotoxicity of each ISCADOR production is standardized in the Yoshida Ascites cell culture test. Other quality and purity criteria of the drug are ensured by specific production and control steps in accordance with GMP.

ISCADOR is intentionally a whole plant extract, as its anticancer activity is bound to the whole protein complex and its native tertiary structure. Cytotoxicity studies with cancer cell cultures demonstrate that fractions of the complex have limited activity and that any separation process may easily destroy the native tertiary structure of the high molecular weight proteins, causing a loss of anticancer activity.

3. TOXICITY

For production control purposes as well as for the general evaluation of toxicity of the drug the LD50 of ISCADOR has been determined. The LD50 of ISCADOR in mice as expressed in mg of fresh plant per kg bodyweight varied from 90 mg/kg when administered i.v.,

to 800 mg/kg when administered s.c. The clinical effects of single toxic dosages of ISCADOR administered to mice consist mainly in ataxia, dysponoea exophtalmia and tonic-clinic cramps.

If the animal dies after the injection of a single toxic dosage it is usually due to circulation collapse.

Further animal toxicity studies such as 13 weeks' chronic toxicity, teratogenicity or any other toxicity study were not undertaken, as the safety of the drug in man is already well documented.

The drug has been used for the treatment of human cancer since 1921 and about 100,000 patients have so far been treated. About 10,000 cases where ISACOR was applied continuously for several years, in most cases longer than 5 years, are completely documented and demonstrate the safety of the drug.

PHARMACOKINETIC STUDIES

Limited pharmacokinetic studies were conducted with a high molecular weight protein fraction of ISCADOR in rats. The main part of the labelled protein fraction, i.e. about 40% of the total detected quantity in the organism, was found in spleen and liver.

Within 41 hours after administration 65% of the protein fraction was excreted.

In tumour bearing animals (Wistar rats) 7% at 17 hours after injection and 4% at 41 hours after injection of the total administered radioactivity was detected in the tumour.

PHARMACODYNAMIC STUDIES

The pharmacodynamnic effect of ISCADOR was studied in a variety of tests using in-vitro and in-vivo test models. By three different approaches, namely by investigations on its direct effect on tumour cell cultures, on its effect on the organism's responsiveness and on its tumour growth inhibiting effectiveness in in-vivo models, the anticancer activity of ISCADOR was demonstrated.

a. Cell culture and serological studies

In two different tumour cell cultures (IgG2B and Yoshida Ascites tumour cells) the selective cytotoxicity of ISCADOR for these cells has been demonstrated. Thymus and spleen cells in the same cell culture were not affected by ISCADOR. In serological tests using Ehrlich carcinoma ascites cells, SA/Ia sarcoma ascites cells and SOV-16 ascites cells, the tumour cells were selectively agglutinated while no agglutination of erythrocytes could be observed.

b. Responsiveness

The activity of ISCADOR on the organism response has been tested in in-vitro tests as well as in in-vivo studies.

- In rats and mice with severely damaged hematopoietic system due to irradiation, the treatment with ISCADOR induces an earlier recovery of the erythropoietic system and does not adversely affect the recovery of the myeloic system.

- The effect of ISCADOR on immunological parameters was investigated involving healthy animals, animals injected with an antigen, and tumour bearing animals.

  In healthy animals ISCADOR itself demonstrated an antigenic effect inducing delayed type hypersensitivity as well as immediate antibody response (Arthus phenomenon). Serological tests failed to demonstrate the formation of anti-ISCADOR antibodies detectable by hemagglutination or precipitation (Ochterlony test). ISCADOR significantly increased the peripheral white count in mice.

  In animals that were injected with an antigen, ISCADOR significantly increased the rise of delayed type hypersensitivity when immunization was done i.c. with the antigen suspended in ISCADOR. An i.c. preinjection of ISCADOR five days before immunization resulted in a further increase of delayed type hypersensitivity. When ISCADOR and the antigen were injected at separate sites or times, no stimulation of the delayed type hypersensitivity to the antigen could be observed. ISCADOR injected i.v. or i.p. induced a significant increased cellular phagocytic activity toward an injected antigen in mice.

  The humoral adjuvanticity of ISCADOR when injected i.p. mixed with the antigen was demonstrated by an accelerated IgM plaque-forming cell response followed by an increase of the IgG and IgA plaque-forming cell response in the Jerne test.

  When the antigen SRBC and ISCADOR were i.p. injected at different times, the response to the antigen stimulus was dependent on the time at which ISCADOR was given in relation to the antigenic stimulus. If ISCADOR was given prior to the administration of the antigen, the antibody formation was depressed; however, if the sequence was reversed, the antibody formation to the antigen was enhanced.

In tumour bearing animals (mice and rats) various studies indicate that ISCADOR may induce hyperplasia of thymus and enhanced blastogenesis of thymocytes (rats). Whether this is due to an unspecific immunostimulation or specifically related to the anticancer effect of ISCADOR cannot be concluded from these studies. A vague trend is seen that under the treatment of ISCADOR an inverse relationship may exist between the degree of thymus hyperplasia and the extent of tumour growth. An unspecific stimulation of lymph node lymphocytes by ISCADOR was demonstrated in the transformation assay utilizing the mitogen concanavallin A.

c. Tumour growth inhibition studies

Various scientists from different research institutes demonstrated the tumour growth inhibiting effect of ISCADOR in several animal model systems implying murine allogeneic tumours, a syngeneic transplantable and a chemically induced one.

In five studies with murine allogeneic model systems utilizing sarcoma 180, the results showed a good agreement with respect to the degree of tumour growth inhibition. If ISCADOR was administered after tumour implantation, the tumour growth was as a rule about 50% compared to non-medicated inoculated control animals. When the drug was administered prior to tumour implantation, the tumour inhibition was even further increased, and in several cases the tumour completely failed to take hold in the host organism.

In a murine model system with a syngeneic transplantable tumour, (Fibrosarcoma) ISCADOR inhibited tumour growth when administered prior to tumour inoculation, however not when only administered after tumour implantation.

In rats exposed to the carcinogen FANFT which is known to induce bladder tumour, a continuous treatment with ISCADOR inhibits significantly the hyperplasted transformation of the bladder mucosa.

d. Tolerance

The studies on thymus hyperplasia and tumour growth inhibition demonstrated that the most responsive level of ISCADOR is clearly not the highest tolerated level, but in the range of 5 to 20% of the LD50 dosage in the animal strain under investigation. Continuous daily treatment with ISCADOR within this range did not cause any clinical toxic symptoms. At higher levels of ISCADOR, thymus hyperplasia and tumour growth inhibition decreased.

6. CLINICAL STUDIES: DESIGN AND EXECUTION

In man the effectiveness and safety of ISCADOR in the treatment of solid cancer was investigated in a variety of clinical studies. These studies included prospective randomized, prospective and retrospective partially controlled (allocation to the treatment groups was not done strictly at random) and open studies with historical control groups. Further, numerous single case studies were examined for corroborative purposes. The studies were conducted mainly by four clinical centers (Basle/Arlesheim, Switzerland; Munich and Herdecke, W. Germany; Vienna, Austria). The institutions were a private hospital, two municipal hospitals and a University hospital respectively.

The clinical studies were usually followed for 5 years and some even longer. The main parameter to measure effectiveness was the five year survival rate. Other parameters were rate of recurrence, safety and general health status depending on the design of the study. In all studies, known prognostic variables (e.g. stage, age, sex, histology) were taken into account. In the prospective randomized studies (controlled studies) prerandomization stratification was not possible due to the limited arrival rate of patients. The comparability of the groups, however, was ascertained by retrospective review of known characteristics influencing the prognosis.

7. RESULTS

In the evaluable studies involving more than 3000 patients, the survival rates of patients treated with ISCADOR were distinctly superior to those of the comparative groups. The usefulness of ISCADOR as an anticancer drug was demonstrated in the studies with the following tumour sites: Cervix, ovary, breast, stomach, colorectum, liver, bladder, bronchus, pleura melanomas. In the following the results of the clinical studies are summarized.

a. CERVIX

Three clinical studies were conducted with this tumour site. One of them was controlled (trial no. 001) and evaluable. In this study the allocation of the patients to the test groups was done arbitrarily according to the first letter of their names. The second study, although controlled, could not be evaluated due to insufficient # of patients and too short a period of observation. The third study (trial no. 003) was an open one to supply corroborative data for the usefulness of the drug.

In the controlled study (trial no. 001) involving 790 patients with cervical carcinoma, stages I to III, ISCADOR was used in a combined therapy with irradiation, whereas radiotherapy alone was applied in the control group. The ISCADOR group had a five year survival rate of 83% compared to 63% in the control group. This difference was statistically significant (P = 1.5% with the single question test by Koller and P = 5% with the x^2-test).

b. CORPUS UTERI

The clinical study with this tumour site could not be evaluated because too few patients were involved and within too short a period of observation (trial no. 005).

c. OVARY

Two open clinical studies with historical control groups (trial no. 005 and 006) were conducted where ISCADOR was used as adjuvant therapy in the treatment of ovarian neoplasm. In trial no. 005 involving 25 patients the five year survival rates were:

100% in stagesI and II, 23% in stage III, and 0% in stage IV. These results compare favorably with a comparable historical control group.

In trial no. 006 involving 32 patients with ovarian carcinoma stage III, the average survival period was 23 months. This also compares favorably with a comparable historical control group.

d. BREAST

Two controlled studies (trial no. 007 and 008), one partially controlled (trial no. 010) and one open clinical study with historical control group (trial no. 009) were conducted to evaluate the effectiveness of ISCADOR when applied as adjuvant therapy in the treatment of mammary carcinoma patients.

In study no. 007 involving 155 (157) patients with mammary carcinoma stagesI to III (III + IV) the distribution to the test groups was strictly random. ISCADOR was used after operation as adjuvant therapy, whereas the control group received combined modality treatment with operation and irradication. The 6 to 9 years survival rates favoured ISCADOR in stage III (III+IV) (24% survived against zero in the control group) whereas in stage I and II no difference could be demonstrated between the two groups.

In the partially controlled study (trial no.010) two groups of patients were used, one consistently treated with ISCADOR (319 patients) as adjuvant therapy and the other inadequately or not treated with ISCADOR (254 patients). Both were in the same hospital and were compared with respect to their 5 year survival rates. These were for the ISCADOR group: stage I: 84%; stage II: 59%; for the control group stage I: 63%; stage II: 41%. The differences were statistically significant and most likely attributable to the drug and not to any imbalance of prognostic factors between the test groups, although the allocations to the test groups were not random.

In the open study (trial no. 009) involving 328 patients, the results achieved with ISCADOR in the treatment of mammary carcinoma patients were compared with those of patients treated at this hospital before ISCADOR was was introduced there. An obvious benefit with regard to prolonged survival rates of the patients was demonstrated for ISCADOR.

Corroborative data on the usefulness of ISCADOR were supplied by a further open clinical study with this tumour site (trial no. 011).

e. STOMACH

One controlled (trial no. 012) and one partially controlled clinical study (trial no. 013) were conducted to determine the effectiveness of ISCADOR as adjuvant therapy in the treatment of stomach carcinoma patients.

In the controlled clinical study where the allocations of the 167 evaluable patients to the test groups were strictly random, three treatments were included: 1. adjuvant treatment with ISCADOR, 2. adjuvant treatment with 5-FU, and 3. no adjuvant therapy. The 2-5 years' interim evaluation of this study demonstrates that the adjuvant therapy with ISCADOR resulted in the highest survival times and rates of the lymph node negative as well as lymph node positive patients compared to those of the other two control groups.

In the partially controlled study (trial no. 013), the adjuvant therapy with ISCADOR in resected stomach carcinoma patients was compared with a control group receiving no adjuvant therapy in the same hospital. The allocation to the comparative group was not random. The ISCADOR patients showed significnatly better five year survival rates, especially in the lymph node positive cases.

f. COLORECTUM

One hundred forty-four patients with colon carcinoma stages I to IV were included in study no. 014 where the usefulness of ISCADOR as adjuvant therapy was determined. The ISCADOR treated patients showed significantly higher 5 year survival rates than the control patients receiving no adjuvant therapy.

A similar type of study was trial no. 015 with rectum carcinoma patients conducted by the same hospital. In this study the difference between the test groups was only statistically significant for patients with lymph node involvement, in which the adjuvant therapy with ISCADOR resulted in superior survival rates.

Another partially controlled study (trial no. 021) involved patients with inoperable colorectum carcinoma stages III and IV. With or without palliative operations, they showed significantly longer survival periods after ISCADOR treatment than comparable untreated patients in the same clinic.

g. LIVER

Corroborative data on ISCADOR's usefulness were supplied by a partially controlled study (trial no. 022) involving 310 patients with liver metastasis.

h. BLADDER

One open study (trial no. 016) was conducted supplying corroborative data on the usefulness of ISCADOR.

i. BRONCHUS

In study 017 the effectiveness of ISCADOR on the 5-year survival rates of 51 operated bronchus carcinoma patients was evaluated under controlled conditions (randomization by sealed envelope). The results of the patients with lymph node involvement allowed no statistical assessment due to the deficient number of evaluable patients in the ISCADOR group (n=4). The results of the patients without lymph node involvement, however, could be statistically evaluated.

The ISCADOR treated patients showed a five year survival rate of 67% as compared to 36% of the control group, a difference being statistically significant ($p<0.05$).

The prospective partially controlled study (trial no. 018) involved 77 patients at different hospitals.

Only the patients in hospital A received adjuvant therapy with ISCADOR whereas those in the other hospitals received no adjuvant therapy. All patients were transferred for surgery to hospital A and operated by the same surgeon. Also the staging was done for all patients by the same pathologist.

A statistically significant ($p<0.01$) prolongation of survival time in the ISCADOR treated group was demonstrated: 6 years survival rate of 38% in the ISCADOR group versus 15% in the control group.

j. MALIGNANT MELANOMA

One open clinical study (trial no. 019) showed the usefulness of ISCADOR in this tumour site.

k. PLEURA

In carcinomatous pleural effusion ISCADOR may be used successfully to dry up the exudate and to induce a remission of tumour cells in the exudate. This was demonstrated in open clinical study no. 020 involving 51 patients.

8. SAFETY

The safety of ISCADOR was usually emphasized by all investigators. Only a few adverse experiences after injection were reported, such as high fever, nausea, local irritations and allergy. In most cases they were controlled by adjustment of the dosage and injection frequency. Bone marrow suppression, changes in liver, renal, cardiac or neurological functions were never reported. In view of the beneficial effects of ISCADOR and in comparison to other commonly used antineoplastic drugs, these adverse effects are negligible.

9. CONCLUSIONS

How far can the results concerning the effectiveness of ISCADOR be generalized? Due to ethical and methodological problems which exist in general when testing any antineoplastic drug, and specifically for the testing of ISCADOR, the individual studies could not be designed so as to allow a generalization of the results without precautions. Each individual study can be criticized because the possibility cannot be excluded that prognostic factors, whether known or not, may not have been equally balanced among the test groups. This, however, is a general problem with all long-lasting trials assessing the effectiveness of anticancer drugs. When the results of such a trial, i.e. the survival rates, are evaluated and published, it is usually 5 to 10 years after the design of the study was made. In the meantime, new experiences and new

facts become available from the enormous worldwide cancer research, which of course could not be taken into account when the design of the study was made. Therefore, from the methodological point of view, each well designed and executed study can be criticized at the time the results are published. This, of course, also applies to the ISCADOR studies and obviously limits the generalization of the results of each individual trial. However, if the results of all the carefully conducted trials with ISCADOR are considered in total, their validity can no longer be doubted. All studies uniformly demonstrate the effectiveness of ISCADOR, and a onesided imbalance of prognostic factors, always in favor of ISCADOR, is unlikely.

It is therefore concluded that ISCADOR may have a beneficial effect on the course of the disease of solid cancer in man.

Based on the experimental investigations and on the clinical studies, ISCADOR is recommended for:

- treatment of inoperable tumours, recurrences and metastasis
- the preoperative treatment of tumours
- the adjuvant therapy of solid tumours
- precancerous conditions when indicated

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