Your work focuses on adrenocortical carcinoma (ACC) – a cancer of the adrenal glands; what are the recurrence and survival rates for patients with this condition?

The recurrence rate in ACC with bad prognostic factors is as high as 70-85 per cent. ACC with good prognostic factors has a much lower recurrence rate in the range of 10-30 per cent, but since this last group represents a minority of ACC patients, a precise estimation is not available. Considering all stages together, the five-year survival rate for ACC patients is around 30-40 per cent, depending on stage at diagnosis and other prognostic factors – first and foremost the proliferation rate of the tumour.

Recurrence has a big impact on survival and represents a progression which often leads to patient death, as in most types of malignant tumours. Preventing or postponing recurrence will therefore lead to prolonged survival.

Why is mitotane a good candidate treatment for adjunctive ACC therapy? What is the main treatment that it accompanies?

Mitotane is the only drug frequently used in an adjuvant setting for this disease. Although no comparative studies with other treatments are available, there have been no other therapeutic tools proposed as reliable alternatives. Currently it is given without combination with other active antineoplastic treatments.

In a study published in 2007 in the New England Journal of Medicine you found evidence of the efficacy of mitotane in adjuvant therapy for ACC. Why is there still debate over the use of mitotane and how will your Efficacy of Adjuvant Mitotane Treatment (ADIUVO) programme help to address the issue?

The study we published was both retrospective and observational, and for this reason it cannot definitively establish that mitotane is active as an adjuvant measure. The study is exploratory in nature and raises the hypothesis that mitotane provides some benefit, but this has to be demonstrated through prospective controlled studies.

ADIUVO is the first prospective, randomised, controlled, open-label, multicentre phase III trial for patients with ACC, and it will hopefully answer one important therapeutic question: will patients at low and intermediate risk of recurrence benefit from an active treatment with mitotane compared with follow-up without any drug?

How are patients selected for entry into the ADIUVO trial?

ADIUVO focuses on patients with low to intermediate risk of relapse defined as: stage I-III ACC (according to European Network for the Study of Adrenal Tumors – ENS@T – classification, 2008); microscopically complete resection, defined as no evidence of microscopic residual disease based on surgical reports, histopathology and postoperative imaging; and low index of proliferation of the tumour.

What steps can be taken to minimise potential adverse effects of mitotane for patients?

Careful clinical follow-up and serial monitoring of mitotane levels in blood are mandatory for satisfactory tolerability of the treatment. Elevated-mitotane concentrations have been associated with serious adverse events, therefore mitotane monitoring is extremely helpful to guide the dose adjustments.

The adrenal gland is essential for hormone production. How is hormonal function maintained in patients who are given adrenolytic mitotane doses?

Replacement therapy is needed to avoid adrenal crisis due to the inhibitory effect of mitotane on the adrenal steroidogenesis and the direct toxic effects of the drug. Either glucocorticoid (cortisol) or mineralcorticoid (aldosterone) steroid replacement may be needed in patients treated chronically with mitotane.

What duration would you expect for adjunctive mitotane therapy if it has an acceptable outcome in a patient? What are your plans for the future of this trial?

According to the protocol, the study duration of adjuvant therapy is two years, but current clinical experience suggests extending treatment duration for a couple of years further in patients with good compliance.

In the future, we will explore the efficacy of mitotane in different patient populations; for example, patients with high risk of recurrence. Ultimately, we hope that molecular biology studies will identify target agents with better safety profiles and increased activity and efficacy compared to mitotane.
The risk of relapse

A phase III clinical trial currently being undertaken by the ADIUVO network is seeking to establish the therapeutic importance of mitotane – a postoperative adjuvant treatment used to prevent relapse in adrenocortical cancer.

ADRENOCORTICAL CARCINOMA (ACC) is a rare form of cancer derived from the cortical part of the adrenal glands. By the time of diagnosis, adrenocortical cancer has usually spread to other organs, and patients rarely survive more than five years from the point of diagnosis. Currently, the best treatment involves surgical resection – the total removal of the affected organ – but even that does not completely prevent progression of the illness. While patients with bad prognostic factors are at very high risk of relapse, those with good prognostic factors have a much lower recurrence rate. Most patients relapse after radical resection, and nearly all of these patients ultimately die as a result of the cancer. In oncology, adjuvant therapies – such as postoperative radiotherapy for the treatment of breast cancer – have been found to reduce the chance of relapse for many patients, but can have side-effects that must be weighed against the risk of relapse before treatment is given. In the case of ACC, the most common adjuvant employed is mitotane, a derivative of the insecticide DDT, which may play a significant role in reducing the risk of relapse for those affected. It is well-established that mitotane is able to destroy the adrenal glands in animal models and inhibit different enzymatic steps of adrenal steroidogenesis.

Despite its established use, the beneficial effects of mitotane have yet to be confirmed through rigorous, evidence-based scientific methods. Some studies have shown a beneficial effect, but there remains some debate over its efficacy due to a lack of studies with sufficient statistical power to definitively characterise the adjuvant's effect.

RETROACTIVE INSIGHTS

This is exactly what the currently ongoing Efficacy of Adjuvant Mitotane Treatment (ADIUVO) clinical trials aim to achieve. These studies, pioneered by Professor Massimo Terzolo of the University of Turin, Italy, seek to conclusively establish mitotane's efficacy as a postoperative adjuvant drug for the prevention of relapse in ACC.

A preliminary study retrospectively considered 177 patients who were treated with radical surgical resection from 1985-2005. In this study, 47 Italian and 75 German patients received mitotane treatment, while 55 Italian and 75 German patients did not receive any postoperative adjuvant treatment. The findings showed that the average recurrence-free survival was longer for those who were treated with mitotane than for those who were not. The median recurrence-free survival rate was 42 months for those given mitotane compared with only 10 months for those who were not.

The second retrospective arm of this research considered how levels of mitotane in the blood after adjuvant treatment correlate with relapse and recovery. Previous studies demonstrated that mitotane levels in the blood of 14 mg/l or higher correlate with tumour response and improved rates of survival in patients with advanced ACC. This study showed that patients whose mitotane levels are ≥14 mg/l survive longer without a recurrence of their ACC after radical resection of their tumour.

Of the 122 patients considered, 63 reached and maintained mitotane levels over 14 mg/l, while 59 did not. Those who reached higher mitotane levels showed a significantly reduced risk of recurrence, although the risk of death was not significantly altered during this study due to the low frequency of deaths. Follow-up studies will clarify this point.

This research also tested two different dose regimens to see how dose affects mitotane levels and how these levels correlate with clinical outcome. High-dose regimens raise the mitotane levels more rapidly than low-dose, but this study did not find an obvious benefit of high-dose regimes. This is crucial when considering the various potential side-effects.

THE ADIUVO TRIAL

These studies, though promising, are retrospective. A further study is needed to better understand mitotane's effects as an adjuvant, especially in low-risk patients for whom the side-effects of mitotane might outweigh the potential benefit. Terzolo is therefore in the process of conducting a multi-centre, randomised, open-label, controlled, prospective phase III clinical trial on mitotane to provide definitive evidence regarding mitotane's effects as an adjuvant therapy. This study should answer the uncertain points that remain after the retrospective study, as randomised controlled trials are the gold standard of evidence-based medicine when it comes to establishing the value of a treatment.

This ongoing project’s primary objective is to compare mitotane adjuvant-treated patients with those who do not receive adjuvant therapy to investigate how this affects the recurrence-free survival time of low-to-intermediate risk patients after resection. It also considers some secondary parameters, including the overall survival rates, time to recurrence, disease-free...
Adrenocortical carcinoma

- A rare cancer, affecting only 1-2 people per million annually
- Shows a bimodal distribution by age, with cases generally appearing in children under the age of five and adults 30-40 years of age
- Due to the effects on hormone production, tumours in the adrenal gland can cause a diverse array of symptoms including Cushing’s syndrome and precocious puberty

survival rates, quality of life, toxicity of the drug and the effects of mitotane on a wide variety of patient subgroups. Patients taking part are split into two equal groups, one treated with orally administered mitotane to maintain 14-20 mg/l of mitotane in blood, the other given no treatment and simply observed throughout the study. This trial began in October 2008 and is currently ongoing, with the main results expected in 2017.

The ADIUVO study is conducted under the endorsement of the European Network for the Study of Adrenal Tumours (ENS@T), an international, multi-centre scientific collaboration. Participant countries include Italy, Germany, France and Canada, and the network currently has many activated centres with 46 patients across North America and Europe. Furthermore, ADIUVO is growing, with a large number of centres recently established in the UK and more across Poland, Sweden and Norway in the process of being activated.

This research is an important step forward for evidence-based treatments. It seeks to provide a solid understanding of a drug that is widely used without firm proof of its effectiveness against ACC. For those at low risk of relapse in particular, it is difficult to judge whether treatment is justifiable, and this work is beginning to rectify this issue by quantifying the benefits of treatment. Beyond the trials themselves, biomaterial collected through the course of the trial will be used for biomolecular studies, providing insights into the basic science underlying disease pathology. Finally, there is potential for using the vast ADIUVO network to investigate other rare diseases, which face similar problems when it comes to drug development and testing.

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