Mitotane for the adjuvant treatment of adrenocortical carcinoma

September 2011

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Summary

The drug and the review
Mitotane is licensed in the UK for the symptomatic treatment of advanced adrenocortical carcinoma (ACC), a rare and aggressive malignancy with a poor prognosis (estimated 5-year survival of 35%). Although its exact biochemical mechanism of action is unclear, it is a known adrenal cytotoxic agent and it can apparently also cause adrenal inhibition without cellular destruction.

The purpose of this review is to summarise the available data regarding the use of mitotane for the adjuvant treatment of ACC – this is an off-label indication.

Background
ACC has an estimated prevalence of 1 per 100,000 population, taking into account all stages of disease. Although it can occur at any age, there appear to be peaks in early childhood and in the fourth to fifth decade of life.

The mainstay of treatment for ACC is surgical resection; this is the only treatment that has consistently demonstrated improved survival. The rates of relapse following surgical resection are however high (around 75-80%) and this has prompted interest in the use of adjuvant therapy in this setting. There are no published prospective, randomised, studies in this setting due to the rarity of ACC; the majority of the available retrospective data are for mitotane.

There is no NICE guidance available on mitotane (Lysodren®) for the treatment of ACC. The Scottish Medicines Consortium has recommended against its use within NHS Scotland; however this considered its licensed indication only.

Guidelines from the National Comprehensive Cancer Network (NCCN) recommend that mitotane be considered for use as an adjuvant therapy following surgical resection of high-grade tumours; they cite the retrospective study discussed in this review as the largest study available to date in support of this indication. An international panel of specialists in the treatment of patients with ACC unanimously stated that patients with potential residual disease and/or Ki67 (measure of proliferative activity) >10% should be offered adjuvant mitotane.

Literature
EMBASE: exp MITOTANE/ AND exp ADRENAL CORTEX CARCINOMA/ [Limit to: Publication Year 2004-Current and Human]; 218 results.
MEDLINE: exp MITOTANE/; AND ADRENAL CORTEX NEOPLASMS/ [Limit to: Publication Year 2004-Current and Humans]
The European Public Assessment Report (EPAR) was used for data published prior to the licensing of Lysodren®.

At the time of licensing in the EU, no prospective, comparative study of mitotane in the treatment of ACC had been conducted. The EPAR notes that the value of mitotane as an adjunct to surgery had not been adequately investigated in an efficacy and safety study and could not be considered as proven; therefore the license was restricted to unresectable ACC.

Summary continued on next page
**Efficacy studies**
A review of the evidence published since the EPAR was produced located a retrospective analysis of mitotane in the adjuvant treatment of ACC – this is the largest study available to date of this intervention.

- The multicentre study included 177 adults with ACC who had undergone complete resection between 1985 and Dec 2003; adjuvant mitotane was routinely used at this time in some centres but not others.
- The cohorts compared consisted of 47 Italian patients who had received adjuvant mitotane (study group), 55 Italian patients who had not (control group 1) and 75 German patients who had not (control group 2).
- Recurrence-free survival was 42 months in the study group, 10 months in control group 1 (p<0.001 versus study group) and 25 months in control group 2 (p=0.005)
- Recurrence was seen in 48.8%, 90.9% and 73.3%, respectively (hazard ratios for recurrence were 2.91 [95% CI 1.77-4.78] for control group 1 versus study group and 1.97 [1.21-3.20] for control group 2 versus study group)
- Median overall survival was 110 months in the study group, 52 months in control group 1 and 67.3 months in control group 2 (p=0.01 for both control groups versus study group)

**Safety**
Gastrointestinal (GI) disorders are the most frequently reported adverse effects of mitotane therapy (10-100% of patients; 15% of those receiving higher doses in the retrospective study had grade 3). Some (e.g. anorexia) may represent the initial central nervous system impairment. Adverse effects affecting the nervous system occur in approximately 40% of patients; 20% of patients receiving higher doses of mitotane in the retrospective analysis experienced grade 3 neurological events. Other central nervous system effects (e.g. memory defects, aggressiveness, central vestibular syndrome, dysarthria, Parkinson’s syndrome) have been reported in the literature. Serious adverse events are linked to cumulative exposure and are more likely to occur when plasma concentrations of mitotane are ≥20mg/L.

**Critical evaluation**
The best data available to support the use of mitotane in the adjuvant treatment of ACC, to prevent recurrence, is limited to a large, retrospective analysis. There is generally a lack of data for any intervention in this setting due to the rarity of ACCs, and the majority of retrospective reports have examined the use of mitotane. There are no standard comparators to mitotane in the adjuvant treatment of ACC.

The retrospective study has the usual limitations associated with a retrospective design and various authors are sceptical over its efficacy, and call for randomised controlled trials to confirm the findings and define which particular patient groups benefit most (the risks of therapy may not outweigh the potential benefits in those at a low risk of relapse). The Phase III ADIUVO study, which is currently recruiting patients, will compare adjuvant mitotane to follow-up only in patients with ACC at low to intermediate risk of recurrence.

**Health Economics**
No published health economic analyses were located.

Based on a median duration of treatment of 29 months (as reported in the retrospective study) and a dose ranging from 1-5g/day, the total cost of treatment per patient can be estimated at £10,368 - £51,900.

**Issues for consideration**
Mitotane is licensed in the UK for the symptomatic treatment of advanced ACC. At the time of assessment, the European Medicines Agency did not consider the data for adjuvant use to be sufficient to warrant approval. The Agency commented that a further study of adjuvant mitotane was unlikely to show a positive effect unless new prognostic factors are identified to select potential responders.

- Since the EMA approval, a large retrospective analysis has been published and this constitutes the best data for adjuvant mitotane published to date. Considering the limitations associated with a retrospective design, is this sufficient evidence on which to base clinical use of a high-cost drug?
- Are there particular prognostic factors that could identify patients who are more likely to benefit from adjuvant mitotane?
- What is the optimum dose of mitotane – are lower doses as effective as higher doses?
- Will therapeutic levels be reached in adequate time to prevent early relapse in those at high risk?

This document reflects the views of the London New Drugs Group and may not reflect those of the reviewers.
Background

Adrenocortical carcinoma (ACC) is a rare aggressive malignancy with a poor prognosis – the estimated 5- and 10-year survival rates are 35% and 20%, respectively (1). It has an estimated incidence of 0.5-2 per million per year, and an estimated prevalence of 1 case per 100,000 inhabitants, taking into account all stages of disease and the survival rates (1, 2). However as many authors acknowledge, the main data on incidence are based on the national Cancer Institute from the 1970s, and this may underestimate the current situation (3).

Around 60% of patients with ACC will present with symptoms due to adrenal steroid hormone excess (cortisol [Cushing’s], aldosterone, androgens, oestrogens) – these are known as ‘functioning’ tumours (4). Non-functioning tumours usually present with abdominal discomfort or back pain caused by the mass of a large tumour (3). Metastatic disease to the lungs, liver, or bone may cause symptoms before the primary diagnosis is made (1).

Although ACC can occur at any age, there appear to be two distinct peaks – in early childhood and in the fourth to fifth decade of life (5). The majority of cases of ACC are sporadic, although they have been observed in association with several hereditary syndromes (e.g. Li Fraumeni syndrome) (4). The underlying mechanism of carcinogenesis in sporadic cases has not been fully elucidated, but it has been shown that mutations of the p53 tumour suppressor gene and alterations at the 11p15 locus occur frequently (4).

According to revised disease classification from the European Network for the Study of Adrenal Tumors, there are four stages of disease: stage I (tumour size ≤5cm without any risk factors; T1N0M0); stage II (tumour size >5cm but no risk factors; T2N0M0); stage III (tumour of any size with at least one risk factor – tumour infiltration, invasion into adjacent organs, venous tumour thrombus in the vena cava or renal vein, or positive lymph node); stage IV (presence of metastases) (6). For non-metastatic disease (stage I-III), removal of the tumour and adjacent lymph nodes is recommended, and removal of adjacent structures (e.g. liver, kidney) may also be required (1, 2).

For those with inoperable tumours, treatment options include resection with or without adjuvant chemotherapy (for low grade tumours) and palliative chemotherapy or radiation (high grade tumours). Chemotherapy is often administered to those patients with an unresectable tumour at presentation or at relapse. Mitotane is the agent most commonly used; others include cisplatin, etoposide and doxorubicin (and others) but these have questionable efficacy results and considerable higher toxicity (1). Palliative surgery in metastatic ACC may have a role in symptom control (2).

Adjuvant treatment of ACC

Although a significant number of patients may present with resectable disease, the rate of relapse following radical resection is high (around 75-80%), even in those with stage I or II disease (5). The reasons for this are at present unknown. Although several potential predictive factors of recurrence in patients who have undergone radical resection have been identified, they are difficult to define due to the great variability in clinical presentation and biological behaviour of ACC (7).

The high rate of recurrence following surgery has prompted interest in, and use of, adjuvant therapy in this setting (5). However due to the rarity of ACCs, there are no published, randomised prospective trials of adjuvant therapy. The majority of retrospective reports have examined the use of mitotane in this setting (4).

The purpose of this review is to look at the available evidence for the use of mitotane in the adjuvant treatment of ACC.

Mitotane

Mitotane, an analogue of the insecticide DDT, was shown to produce adrenal atrophy in dogs in 1948 and has been used for the treatment of ACC since 1960 (1). It is an adrenal cytotoxic agent, although it can apparently also cause adrenal inhibition without cellular destruction. Its biochemical mechanism of action is unclear; the available evidence suggests that it modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex (8). Mitotane (Lysodren®) is licensed in the UK for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) ACC. The effect of Lysodren on non-functional adrenal cortical carcinoma has not been established (9). Mitotane is not licensed for the adjuvant treatment of ACC.

For its licensed indication, mitotane is initiated at 2-3g daily and increased progressively until plasma levels reach the therapeutic window (14-20mg/L). It has been shown that this therapeutic window represents optimal use of mitotane – balancing the risks of serious undesirable effects (more likely to occur at higher plasma levels) with that of efficacy (there is weak evidence to suggest that plasma levels >14mg/L may result in enhanced efficacy) (9). As the drug accumulates in adipose tissue, therapeutic serum levels are not achieved until around 12-14 weeks following initiation of therapy (10). Mitotane plasma levels should be monitored both initially and once the optimal maintenance dose is reached (specific monitoring recommendations are included in the SPC). As it increases the clearance of exogenously administered steroids, replacement hydrocortisone doses need to be increased (10).

Mitotane was granted orphan drug designation by the European Commission in 2002, based on the low prevalence of the disease. It was used and prescribed in compassionate use programmes in several EU member states, prior to its first marketing authorisation (as Lysodren®) in 2004 (1).

Mitotane – evidence considered at the time of EU marketing authorisation

The Scientific Discussion (European Public Assessment Report) for the approval of Lysodren® notes that no clinical efficacy and safety studies had been conducted by the manufacturers, and that the available clinical information on its use in ACC comes from published reports of uncontrolled studies.
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No prospective comparative study assessing efficacy and safety of mitotane in a well-defined protocol has been carried out. A literature search conducted for the marketing authorisation application located 220 articles published after 1990 and these encompass experience in more than 500 patients followed for various time periods. In the majority of cases the formulation of mitotane used was not reported (1).

The assessment of mitotane efficacy is limited by the difficulties associated with an uncontrolled study design. The EPAR notes that it is also difficult to compare the results of the different studies due to differences in efficacy measures, the stage of the disease (response is dependent on this), the time of treatment initiation (at the time of surgery or later), associated treatments used, and the dose regimen employed.

The available clinical data deemed to be most pertinent is summarised in a table in the EPAR. Other publications are available in the literature but relate to series published before 1990 and have not been included since they did not add anything additional in terms of efficacy or safety to the more recent data (1). The data published at the time was insufficient to support any effect of mitotane on survival – five of nine studies reporting such data found an increase in survival (only with plasma levels exceeding 14mg/L) whereas the other four did not (9, 10).

The Scientific Discussion notes that two papers studying the effects of mitotane as a true adjuvant treatment found no clear-cut evidence that it can increase the disease-free interval and delay the onset of recurrence. One of these was a prospective evaluation of Lysodren either as a treatment of unresectable adrenal carcinoma or as an adjuvant treatment, with monitoring of plasma levels of mitotane. The authors found an obvious effect of Lysodren on survival and tumour regression for unresectable tumours, but no effect when used as an adjuvant treatment. They conclude that a further trial is unlikely to show a positive effect of adjuvant treatment unless new prognostic factors are identified to select potential responders, or a new means to detect micrometastases becomes available (1).

Although some of the publications provided by the manufacturer in the marketing application suggest that adjuvant mitotane may be associated with an improved survival, the available evidence (corroborated by the wide range of publications on this issue) suggests that its value as an adjunct to surgery has not been adequately investigated in an efficacy and safety study and cannot be considered as proven. The licensed indication has therefore been restricted to unresectable adrenal carcinoma (i.e. no possible surgical removal of tumour or metastases, or incomplete removal of tumour and/or metastases) (1).

Data on adjuvant mitotane published since the EPAR

A recent publication seeking to describe how ACC is currently being treated in the UK included a series of 30 patients treated at one of three specialist centres (Newcastle, Cardiff, and Sheffield). The authors report that adjuvant mitotane was being used commonly. Of the 83% of patients who underwent adrenalectomy, the majority (64%) received treatment with mitotane (20% in combination with chemotherapy). (2)

A review article reported that the use of mitotane in the adjuvant treatment of ACC has declined in recent years, given its recognised toxicity and the lack of clear evidence for a beneficial effect (7). The results of the largest retrospective cohort so far, with follow-up for up to ten years, have since been published.

Terzolo et al conducted a retrospective analysis to study the effects of mitotane in the adjuvant treatment of ACC (11). It included adult patients with ACC who had undergone radical surgery (with complete resection) at tertiary referral centres in Italy between Jan 1985 and Dec 2003 – as adjuvant treatment with mitotane was used routinely in some centres but not others, they had the opportunity to compare these two cohorts. To control further for potential biases, they used an additional control group consisting of a cohort of German patients (derived from the German Adrenocortical Carcinoma Registry) who were treated with surgery only (between 1985 and 2005). The primary outcome was recurrence-free survival in those who received adjuvant mitotane compared to those who had not; secondary endpoints included overall survival and adverse events associated with mitotane therapy.

A total of 177 eligible patients were identified, 47 Italian patients who had received mitotane (study group), 55 Italian patients who had not (control group 1) and 75 German patients who had not (control group 2). The median follow-up times after surgery were 56.7 months, 67.6 months and 43.0 months, respectively. The mitotane group and control group 1 were evenly distributed with respect to tumour stage (around 64% stage I or II), whereas control group 2 had a higher proportion of stage I or II tumours (84%). The main results were as follows:

- Recurrence-free survival was significantly longer in the study group (median of 42 months) compared to both control groups (10 months for group 1 [p<0.001] and 25 months for control group 2 [p=0.005]).

- Documented recurrence was 48.8% in the study group compared to 90.9% in control group 1 and 73.3% in control group 2. Hazard ratios for recurrence were 2.91 (95% CI, 1.77 to 4.78; P<0.001) and 1.97 (95% CI, 1.21 to 3.20; P=0.005), respectively. The hazard ratios for the control groups versus the mitotane group were still significant (and higher) when adjusted for age, sex and tumour stage (HR 3.79 and 2.93, respectively).

- Death from ACC was seen in 25.5% of the mitotane group, 54.5% of control group 1 and 41.3% of control group 3. The median overall survival times were 110 months, 52 months and 67 months, respectively (p=0.01 for both control groups versus mitotane). The hazard ratios for the control groups versus the mitotane group (adjusted for age, sex and tumour stage) were 2.47 (95% CI 1.26-4.85) for control group 1 and 1.96 (95% CI 1.00 to 3.87) for control group 2.

- There was no significant difference in efficacy between patients receiving mitotane 1-3g daily and those receiving 3-5g daily, however adverse effects were significantly more common in the high dose group (15% had grade III gastrointestinal events and 20% had grade III neurological events).
The authors conclude that although their study has limitations, it demonstrates a significant benefit from adjuvant treatment with mitotane after surgery for adrenocortical carcinoma.

They acknowledge the limitations of such a non-randomised study, including potential selection bias, diagnostic bias, stage migration and bias in follow-up or ascertainment of outcome. To reduce bias in the Italian cohorts, they included all consecutive eligible patients at a given centre, and the choice to treat/not treat with adjuvant mitotane was based on specific management algorithms in use at the centres, not on the basis of individual characteristics. The uneven distribution of unmeasured characteristics not known to affect prognosis could not be entirely excluded (the only uneven distribution of known or potential prognostic factors measured was a higher proportion of male patients in control group 1, but this was not found to be an independent predictor of survival).

An accompanying editorial discusses the study (12). The author notes the rarity of and limited effective treatments for this tumour. He comments that there is controversy over the efficacy of mitotane, and that the trial data are inconclusive. While this study is retrospective and thus has inevitable limitations, it appears to have been done as robustly as possible and therefore has credibility. He discusses possible reasons why response to mitotane should vary, and notes that it requires metabolic activation. As some tumours may not activate it because of alterations in the process involved, there could be a role for susceptibility testing in advance of treatment. Overall, they comment that this trial provides the best evidence so far, and a ‘compelling rationale’, for the use of adjuvant mitotane following radical surgery for ACC (when the resection has been macroscopically complete), and its observation that lower doses seem to be as effective as higher ones is useful. The author comments that well designed, prospective, randomised trials are needed in this area – however the rarity of ACC and the time it would take to collect sufficient data would require a lengthy, multicentre study. Meanwhile, well-designed retrospective studies are the best data available upon which to make treatment decisions (12).

In a letter commenting on this study, the authors describe the results of a cohort of patients with ACC who underwent complete tumour resection at their centre (n=166), around half of whom (52%) received adjuvant mitotane. Univariate analysis showed that disease-free survival was not improved in those receiving mitotane (no further details of the results are supplied). Multivariate analysis indicated a number of factors associated with shorter disease-free survival: older age, higher disease stage, and cortisol secretion. Mitotane administration was not found to be associated with disease-free survival, although there was a trend towards a benefit in those with cortisol-secreting tumours (13).

In a response to this letter, Terzolo et al suggest that it was likely that the patients receiving mitotane in this cohort were selected for unfavourable prognostic factors, and that selection bias may have contributed to the lack of efficacy of adjuvant mitotane (14).

A further Commentary article offers a ‘skeptical’ view on the efficacy of mitotane in the adjuvant treatment of ACC, highlighting what the authors ‘believe to be several important limitations to the above study (the study authors defend their research against these criticisms in a subsequent letter) (15). They say that the results do not support a recommendation for adjuvant mitotane in all patients; however they agree that it should be considered in selected patients with completely resected ACC and poor prognostic factors including (but not limited to) those that comprise the Weiss score. They go on to discuss the issue of dosing, and suggest that physicians should consider using lower doses that eventually reach therapeutic plasma levels, so that therapy can be sustained for as long as possible. They consider it more likely that mitotane delays growth (rather than being cytotoxic) and so continuing therapy (and not needing to stop it due to toxicity) could in fact prolong survival (15).

In response, Terzolo et al comment that the indefinite continuation of mitotane represents an interesting theory. However they say that a low-dose regimen may not be fully coherent with the concept of adjuvant therapy, because it may take over 6 months to reach therapeutic plasma levels in some, and recurrences occur in a significant proportion of people within six months. They conclude that the heterogeneity in tumour biology that is responsible for the discrepancies in outcome among treated patients needs to be understood, and acknowledge that randomised trials are the only way this can be done. In light of this, they have designed a clinical trial (ADIUVO) that will compare adjuvant mitotane to follow-up only in patients at low to intermediate risk of recurrence (16).

Fassnacht et al conducted a study to determine whether (and to what extent) survival rates for ACC are influenced by patient selection and early specialised care (17). They used data from the German adrenocortical carcinoma registry to compare patients with stage II ACC who were followed up prospectively (i.e. enrolled within four months of resection of the primary tumour; n=30) and those followed up retrospectively (registered >4 months after primary surgery; n=119). The prospective group was found to have a lower recurrence rate (30% versus 74%; p<0.01) and a higher 5-year survival rate (96% versus 55%; p<0.05) – the authors say this is most likely due to a major referral bias in previously reported patient series. The use of adjuvant mitotane was higher in the prospective group (53% versus 16%; p<0.001) and its use was found to be associated with improved survival (hazard risk 0.35; 95% CI 0.13-0.97; p=0.04). The authors postulate that early counselling by a specialist leading to an increased use of adjuvant mitotane may also have contributed to the observed differences in recurrence rate and survival. [Of note – the survival advantage seen in the prospective group persisted when only those who had not received mitotane were analysed]. The authors conclude that their results suggest a referral bias in previously published series (including from their own registry) has led to over-representation of patients with recurrent disease and poor outcome, whereas patients cured by surgery alone may have been grossly under-represented.

**Guidelines/consensus statements**

The Scottish Medicines Consortium (SMC) issued advice on Lysodren in 2006, recommending against its use within NHS Scotland for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (no advice on unlicensed adjuvant use was issued). The SMC concluded that the result of the economic model submitted by the manufacturer was driven in part by an assumed survival advantage, which the data
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London Cancer New Drugs Group—APC/DTC Briefing

Guidelines from the National Comprehensive Cancer Network (NCCN) recommend that mitotane be considered for use as an adjuvant therapy following surgical resection of high-grade tumours. The guidelines cite the study discussed above – it states that this is the largest published retrospective study to date examining the use of mitotane in this scenario (4).

An international panel of specialists in the treatment of patients with ACC discussed the use of adjuvant mitotane at the Second Annual International Adrenal Cancer Symposium in 2008 (18). The panel unanimously stated that patients with potential residual disease and/or Ki67 (measure of proliferative activity) more than 10% should be offered adjuvant mitotane, whereas such is not considered mandatory in the following patients:

- Stage I or II disease
- Histologically proven R0 resection (no residual disease)
- Ki67 expressed in ≤10% of neoplastic cells

The panel did not reach a unanimous position on whether patients with stage III ACC with R0 disease after surgery should receive adjuvant mitotane in routine clinical practice (18).

Another publication summarised the results of a previous consensus conference – no specific recommendations regarding adjuvant treatment were made. The review states that the benefits of adjuvant therapy have not been established; however published reports suggest benefit from low-dose mitotane. Prospective studies randomising patients to surgery ± mitotane with a primary outcome of time to first recurrence are recommended. They include a recommended protocol for mitotane use, as follows (19):

- Begin with 2g/day and increase to achieve plasma concentrations of 14-20mg/L. The target levels may be unattainable because of side-effects, in which case the dose should be adjusted according to tolerance.
- Monitor patients clinically and by measuring adrenocorticotropic hormone (ACTH)/urinary free cortisol/electrolytes
- Adjust the dose of cortisol replacement to assure adequate adrenal replacement
- Monitor and correct as necessary thyroid function, serum testosterone and lipids
- Provide vigorous antiemetics and other supportive therapies

A more recent review article on the management of ACC discusses the use of mitotane as a chemotherapeutic agent in this disease. The author says that the results reported by Terzolo et al should be viewed cautiously, but that the possibility that a longer duration of administration may have had a greater benefit cannot be excluded. The lack of convincing evidence and the difficult in administering therapeutic doses have led to the recommendation that adjuvant mitotane be used only in patients with a high likelihood of recurrence (those patients with large tumours with many of the features that comprise the Weiss score) and small or questionable surgical margins. The optimal duration of mitotane therapy remains unknown (10).

Safety

The adverse events associated with mitotane reported in the retrospective analysis are detailed in Table 1. Temporary dose reduction or discontinuation was necessary in four patients receiving the higher doses and two patients receiving lower doses. The authors acknowledge that low-grade side-effects may have been under-reported, due to the retrospective nature of the study (7).

### Table 1: Adverse events reported in the retrospective study

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade</th>
<th>(no of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>4</td>
<td>2 0 0</td>
</tr>
<tr>
<td>Asthenia or fatigue</td>
<td>17</td>
<td>6 1 0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8</td>
<td>5 0 0</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>13</td>
<td>10 3 0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20</td>
<td>7 0 0</td>
</tr>
<tr>
<td>Elevated GGT</td>
<td>23</td>
<td>10 7 0</td>
</tr>
<tr>
<td>Elevated AST or ALT</td>
<td>19</td>
<td>4 0 0</td>
</tr>
<tr>
<td>Confusion</td>
<td>4</td>
<td>5 2 0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>1 4 0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>4</td>
<td>5 4 0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>1 0 0</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>3</td>
<td>1 0 0</td>
</tr>
</tbody>
</table>

Cost

The median duration of treatment reported in the retrospective analysis was 29 months, with 20 patients receiving treatment with 3-5g daily and 27 receiving 1-3g daily.

Based on a dose of 1-5g of mitotane daily, the cost of 28 days’ treatment would be £330 - £1,652. Based on the median treatment duration seen in the retrospective study (29 months), the total cost of treatment per patient would be £10,368 - £51,900.
## Issues for consideration

Mitotane is licensed in the UK for the symptomatic treatment of advanced ACC. At the time of assessment, the European Medicines Agency did not consider the data for adjuvant use to be sufficient to warrant approval. The Agency commented that a further study of adjuvant mitotane was unlikely to show a positive effect unless new prognostic factors are identified to select potential responders.

- Since the EMA approval, a large retrospective analysis has been published and this constitutes the best data for adjuvant mitotane published to date. Considering the limitations associated with a retrospective design, is this sufficient evidence on which to base clinical use of a high-cost drug?

- Are there particular prognostic factors that could identify patients who are more likely to benefit from adjuvant mitotane?

- What is the optimum dose of mitotane – are lower doses as effective as higher doses?

- Will therapeutic levels be reached in adequate time to prevent early relapse in those at high risk?

The document reflects the views of LCNDG and may not reflect those of the reviewers

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References:

9. Scottish Medicines Consortium: Mitotane 500mg tablets (Lysodren®) Advice 328/06 (December 2008). Accessed online via: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/Mitotane_Lysodren/mitotane_500_mg_tablets_Lysodren