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Short Communication

# Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis

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ABSTRACT

*Background:* Aggressive fibromatosis (AF) or desmoid tumour is a monoclonal proliferation which is locally invasive but does not metastasize. If local treatment fails to control the disease, systemic treatment with anti-oestrogens, non-steroidal anti-inflammatory drugs (NSAIDs) or chemotherapy can be used. Recent reports indicate that pegylated liposomal doxorubicin (PLD) is effective.

*Methods:* Twelve patients with AF received PLD between February 2006 and May 2009. PLD was administered intravenously (iv) at 50 mg/m$^2$ over 1 h every 4 weeks.

*Results:* The female/male ratio was 11:1 and median age at presentation was 29 years (range 3–53). Objective response (PR) was achieved in 4 (36%) of 11 patients. In one case ongoing shrinkage of the tumour was observed for over 12 months and partial remission was achieved at 14 months after the completion of treatment. Seven patients achieved stable disease. One patient is currently undergoing chemotherapy. Clinical benefit in terms of pain relief, improved mobility or cosmesis was observed in 11 patients. Nine patients (75%) had no evidence of progression at the end of this follow-up period and disease control has ranged from 7 to 39 months with a median of 14 months. The most severe toxicities observed were palmar-plantar erythema (4) and mucositis (3). In 6 cases (55%) toxicity resulted in dose reduction.

*Conclusion:* This is the largest series of patients with AF receiving PLD reported to date. PLD as a single agent therapy has acceptable toxicity and highly promising activity in unresectable AF and may provide long-term clinical benefit in some patients.



## 1. Introduction

Aggressive fibromatosis (AF) or desmoid tumour is a rare entity with an incidence of 2–4 cases/million/annum.[1] Although these tumours do not metastasize they demonstrate an aggressive clinical behaviour because of their highly invasive nature. Local infiltration can result in debilitating pain and deformity and in some cases life-threatening organ damage.

Aggressive fibromatosis may be sporadic or associated with familial adenomatous polyposis (FAP), an autosomal dominant syndrome caused by mutations in the adenomatous polyposis coli gene (APC). FAP-driven AF is usually related to inactivation of the APC gene whereas sporadic AF is usually associated with mutations in the beta-catenin gene *CTNNB1*, resulting in increased nuclear expression of beta-catenin, an important diagnostic feature.

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The management of AF has remained largely unchanged over the last decade. Surgery with clear margins is the mainstay of treatment.[2,3] Radiotherapy may be offered when the surgical margins are involved or if repeat surgery is difficult. If surgery and radiotherapy are not applicable or fail to control the disease, systemic treatment is used. Hormonal agents (anti-oestrogens and aromatase inhibitors) and/or non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated modest activity with response rates ranging between 15% and 30%.[4,5] A variety of chemotherapy regimens are reported to have activity including weekly methotrexate/vinblastine[6,7] and doxorubicin/dacarbazine.[8,9] However, their use is often limited by toxicity. Single agent pegylated liposomal doxorubicin (PLD) has recently been reported to have efficacy but also acceptable toxicity.[10]

PLD is doxorubicin hydrochloride (a topoisomerase II inhibitor) encapsulated in liposomes coated in polyethylene glycol, minimising uptake by the reticuloendothelial system and prolonging the elimination half-life. Its toxicity profile is favourable compared with that of conventional doxorubicin, and the incidence of cardiotoxicity is significantly lower.[11] Wehl et al.[10] reported that 4 patients (3 children, 1 adult) with advanced AF receiving PLD at 20–50 mg/m$^2$ 3-weekly responded well to treatment without suffering significant toxicities.

Here we present the results of our experience with PLD in twelve adult patients with AF. This is the largest series of patients with AF receiving PLD reported to date.

## 2. Patients and methods

Between February 2006 and May 2009 12 patients with progressive or recurrent AF received PLD at a starting dose of 50 mg/m$^2$ as a 1 h IV infusion every 28 d. Dose reductions or delays were performed as indicated according to haematological or clinical toxicity.

### 2.1. Response assessment

Disease status was assessed by clinical examination and imaging (computed tomography or magnetic resonance imaging). The RECIST assessment system was used to evaluate radiological response.[12] Changes in disease-related symptoms (e.g. pain, limitation of movement) were monitored closely.

### 2.2. Toxicity assessment

Haematological toxicity and other side-effects were graded using the National Cancer Institute Common Toxicity Criteria and were documented during each cycle of treatment. They were managed according to departmental protocols for chemotherapy-related toxicity.

### 2.3. Follow-up

Following the completion of treatment patients remained under regular follow-up comprising clinical/symptomatic and/or radiological assessment of their progress. The current report includes all the available follow-up data until May 2009.

### 2.4. Statistics

Results were analysed using descriptive statistics. Median and range were used for continuous variables and proportions (%) for categorical variables.

### 2.5. Ethical approval

The study was reviewed and approved by the Royal Marsden Hospital Clinical Audit Committee.

## 3. Results

### 3.1. Patient characteristics

The female/male ratio was 11:1. The median age at presentation was 29 years (range 3–53). The primary sites of disease included: limbs (3), abdomen (2), chest wall (2), head and neck (1), perineum (1), brachial plexus/upper thorax (1), brachial plexus/axilla (1) and back/paraspinal area (1). The predominant symptom at baseline was pain in 10 of the 12 patients (83%).

### 3.2. Previous treatment

The details are summarised in Table 1 (treatment received prior to PLD).

### 3.3. Treatment duration

The median number of cycles completed was 6. One patient had to discontinue treatment at cycle 4 and two at cycle 5 due to toxicity. One patient discontinued at cycle 4 for personal reasons (moved abroad).

### 3.4. Response

Objective response (PR) according to RECIST was achieved in 4 (36%) of 11 patients. In 2 cases the response was noted within 3 months of completion of treatment and in the third case 5 months later. In the fourth patient, ongoing shrinkage of the tumour was observed for over 12 months and partial remission was not achieved until 14 months after the completion of treatment. In 7 (64%) patients the best response was stable disease. One patient is currently undergoing chemotherapy and both symptoms and disease status after 4 cycles are stable. Clinical benefit in terms of pain relief or improved mobility and cosmesis was observed in 11 patients. Three (27%) patients have so far progressed after treatment and their time to progression calculated from the start of PLD ranged from 9 to 14 months. The remaining 9 patients (75%) had no evidence of progression at the end of the follow-up period for this study and the duration of disease control in this group thus far ranges from 7 to 39 months with a median of 14 months.

**Table 1 – Treatment received prior to PLD.**

| Patients | Primary site | Previous operation(s) (op(s)) | Previous radiotherapy (RT) | Previous systemic treatment |
|---|---|---|---|---|
| 1 | Perineum | 6 Ops: at presentation, resection of residual disease and 4 debulking ops for recurrence | – After original resection to perineum (60 Gy in 30#)<br>– To recurrence in L thigh | – For recurrence: Tam/Predn/Cyclo/MTX for 3 mo – no response<br>– For recurrence: ifosfamide × 4 SD |
| 2 | Back- paraspinal area | 8 Ops: at presentation and debulking for recurrence | – To recurrence in back (56 Gy in 28#)<br>– To recurrence in breast (56 Gy in 28#) | – Toremifene for 3 mo PD,<br>– MTX/vinblastine for 6 mo SD,<br>– Imatinib for 3 weeks PD,<br>– Rechallenge with MTX/vinblastine for 4 mo SD |
| 3 | Lower limb | Inoperable | None | – Sulindac/vit C > 12 mo SD,<br>– Imatinib for 12 mo SD |
| 4 | Head and neck | Inoperable | None | Diclofenac for 8 mo PD |
| 5 | Abdomen | 2 Ops: at presentation and debulking for recurrence | 2001 (details unavailable) | Tamoxifen <2 mo – PD |
| 6 | Axilla/brachial plexus | Inoperable | None | Tamoxifen – no response |
| 7 | Upper limb | 1 Op at presentation | None | Tamoxifen pre-op failed |
| 8 | Chest wall | Inoperable | None | Tamoxifen 2 mo – minimal response |
| 9 | Abdomen (Gardner's) | 2 Ops: at presentation and debulking for recurrence | None | Tamoxifen and sulindac-poor tolerance |
| 10 | Upper limb | Inoperable | None | Diclofenac for 3 mo, tamoxifen for 6 mo – PD |
| 11 | Upper thorax/brachial plexus | 1 Op at presentation | To primary site following surgery (56 Gy in 28#) | Tamoxifen for 16 mo for recurrence – SD but ongoing pain |
| 12 | Chest wall | 1 Op at presentation | None | Tamoxifen & diclofenac for 5 mo PD |

*Abbreviations*: SD, stable disease; PD, progressive disease; Cyclo, cyclophosphamide; MTX, methotrexate; Op(s), operation(s); Mo, months.

### 3.5. *Toxicity*

The most severe toxicity observed was palmar-plantar erythema (PPE) grade 3 (1) and grade 2 (3) as well as mucositis grade 2 (3). Fatigue grade 2 (1) was also reported. In 6 cases (55%) toxicity resulted in dose reduction. No grade 3/4 haematological toxicity was observed.

## 4. Discussion

Despite their retrospective nature and the small number of patients involved, many studies investigating the outcome of chemotherapy in AF have shown some clinical benefit and durable disease control lasting for months to years. The toxicity of chemotherapy is clearly a concern, especially if likely to be chronic (neuropathy), cumulative (cardiotoxicity) or associated with a risk of cancer (cyclophosphamide). Less toxic, safer agents are clearly required.

In this study, PLD has been shown to have activity against AF without causing serious toxicity. Notably the majority of patients had clinical benefit in the form of pain control, improved mobility or cosmetic improvement (associated deformity). Objective response was documented in 36% of cases. In the remainder the disease remained stable by RECIST although in 4 cases minor disease shrinkage did occur. Evaluation according to RECIST is often difficult owing to the infiltrative nature of the disease and its complex association with adjacent anatomical structures. Alterations in contrast enhancement, indicative of a favourable response may herald symptomatic benefit, although this can be considerably delayed.

With regard to toxicity, most patients tolerated 6 cycles of chemotherapy, although a dose reduction was required in 50% of the cases. In 42% of the cases the dose was reduced from 50 mg/m$^2$ to 40 mg/m$^2$ (and in one case from 40 mg/m$^2$ to 35 mg/m$^2$) suggesting that the optimal dose lies between 40 and 50 mg/m$^2$. No cardiotoxicity or significant haematological toxicity was noted. Mucositis and PPE were the most severe side-effects but with appropriate treatment and dose modifications they were managed successfully.

The study sample is small but it is noteworthy that none of the patients progressed while on PLD and although follow-up is relatively short, some of the ongoing responses are encouragingly durable (>1 year in 4 patients, >2 years in 1 patient), especially considering that the majority of the patients had progressed within 6 months of starting treatment with hormonal agents (±NSAIDs).

The optimum duration of treatment is unresolved. We empirically planned to administer 6 cycles in patients with stable or responding disease based on routine practice with chemotherapy for malignant conditions. Based on the observation that response may be slow, some clinicians favour prolonged administration of chemotherapy (>6 months) in AF.[13,14] The fact that we have observed prolonged benefit and late responses suggests that prolonged therapy is unnecessary and is likely to result in undesirable side-effects with no additional benefit.

The limitations of a retrospective analysis of a small number of patients are acknowledged. These patients are markedly heterogeneous in terms of disease extent, disease site and number of prior therapies. Follow-up is short and further evidence is required in order to determine the value of PLD relative to other systemic approaches. Recent reports of activity with imatinib in AF[15] suggest that small molecule inhibitors of targets such as platelet derived growth factor receptor (PDGFR) need to be explored further, possibly in comparison with chemotherapy.

This study provides evidence of activity of single agent PLD in the management of AF. Prospective randomised studies are required to define whether it is superior to other chemotherapeutic or molecularly targeted agents but based on the results of this study it is clear that PLD has promising activity in refractory AF and may provide long-term clinical benefit in this disease.

## Conflict of interest statement

None declared.

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