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Original Research

Patient-derived solitary fibrous tumour xenografts predict high sensitivity to doxorubicin/dacarbazine combination confirmed in the clinic and highlight the potential effectiveness of trabectedin or eribulin against this tumour☆

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Abstract ***Background:*** Preclinical models that mimic pathological and molecular features of solitary fibrous tumour (SFT) represent an important tool to select effective regimes and novel compounds to be tested in the clinic. This study was aimed at developing two preclinical models of SFT, assessing their predictive value in the clinic and selecting potential novel effective treatments.

Material and methods: Two dedifferentiated-SFT (D-SFT) models obtained from patients' biopsies were grown in immunodeficient mice. The antitumour activity on these models of doxorubicin, dacarbazine (DTIC), ifosfamide (monotherapy or combination), trabectedin and eribulin was tested. Twelve SFT patients were treated with doxorubicin and DTIC. Response by RECIST, progression-free survival and overall survival were retrospectively evaluated, distinguishing malignant-SFT (M-SFT) and D-SFT.

Results: Two D-SFT patient-derived xenografts (PDXs) that represent the first available preclinical *in vivo* models of SFT were developed and characterised. Doxorubicin/DTIC, DTIC/ifosfamide, doxorubicin/ifosfamide combinations consistently induced better antitumour activity than the single-agents. Particularly, doxorubicin/DTIC combination caused a max tumour volume inhibition >80% in both models. Doxorubicin/DTIC combo showed activity also in the case-series. Best RECIST responses were: 6 responses (M-SFT = 2 of 7, D-SFT = 4 of 5), 1 stable disease, 5 progressions, with a 6-month median progression-free survival (M-SFT = 6, D-SFT = 10 months). The PDXs were very sensitive to trabectedin and eribulin.

Conclusion: Doxorubicin plus DTIC combination was effective in our two D-SFT mice models and appeared to be active also in the clinic, especially in high-grade D-SFT patients. Among additional drugs tested in the PDXs, trabectedin and eribulin were highly effective, providing a rational to test these drugs in D-SFT patients.

1. Introduction

Solitary fibrous tumour (SFT) is a rare sarcoma [1,2], marked by a recurrent *NAB2-STAT6* gene fusion that is responsible for the nuclear expression of the transcription factor STAT6 [3]. Three clinical-pathologic variants of SFT are identified: typical (T-SFT), malignant (M-SFT) and dedifferentiated (D-SFT) SFT [1,4]. M-SFT is marked by a greater mitotic index (≥4/10 HPF) compared with T-SFT. D-SFT shows the transition to a high-grade morphology. Notably, STAT6 nuclear immunopositivity can be lost in D-SFT [5]. SFT has a low metastatic potential (≤15%), but a greater metastatic rate (40%) is observed in D-SFT [6,7].

Preliminary evidence is available that both anthracyclines and temozolomide are effective in SFT [8,9]. We had already tested the activity of temozolomide and dacarbazine (DTIC) in a patient-derived xenograft (PDX) model of high-grade SFT, confirming that they looked equally active [10]. In the same paper we reported 8 patients undergoing DTIC, with 3 responses.

The good consistency observed between preclinical and clinical observations encouraged us to develop further this approach. In this study, we report the development and characterisation of two preclinical models of SFT and the results of the experiments aimed at comparing the activity of cytotoxic agents currently used for treatment of soft tissue sarcoma, including the doxorubicin-DTIC combination, trabectedin and eribulin. We also assessed retrospectively the clinical activity of doxorubicin in combination with DTIC in a small population of advanced SFT patients.

2. Materials and methods

2.1. Experimental models and pharmacological studies

Two D-SFT PDX models were used in the study.

2.1.1. Development and characterisation of the model

The models were established by subcutaneous grafting of tumour fragments obtained at the time of surgery from 2 patients into the right flank of female SCID (SFT-1) or nude (SFT-2) mice (Charles River, Calco, IT). Specifically, SFT-1 was established from a pleomorphic osteochondro-like D-SFT from a patient with recurrent pelvic D-SFT [4]. Both in the patient and in the PDX, the tumour carried the *NAB2-STAT6* fusion transcript (ex6.INT6.ex3int), as detected by RT-PCR [3], but lacked immunohistochemical nuclear STAT6 expression [5]. SFT-2 was derived from a patient with locally relapsed D-SFT, pre-treated with sunitinib. This tumour closely resembled an Ewing sarcoma/peripheral primitive neuroectodermal tumour [4]. It was characterised by *NAB2-STAT6* fusion transcript (ex6.ex18) and negative STAT6 immunohistochemistry [5]. This