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Clinical Trial

Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: Final results of a phase II study of the German Interdisciplinary Sarcoma Group (GISG)

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KEYWORDS
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Abstract ***Background:*** Desmoid tumours describe a rare monoclonal, fibroblastic proliferation characterised by an often unpredictable clinical course. Surgery is one therapeutic option for progressing patients, except if mutilating and associated with considerable function loss.

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Nilotinib;
Positron emission tomography;
Progression arrest

Different systemic treatment approaches have been investigated and promising results could be demonstrated using imatinib.

Patients and methods: We initiated a phase II trial within the German Interdisciplinary Sarcoma Group (GISG) evaluating imatinib to induce progression arrest in desmoid tumour patients being Response Evaluation Criteria in Solid Tumours (RECIST) progressive, not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss (NCT01137916). Thirty-eight patients (median age 44 years [range: 19–80]; 68% female; 90% Eastern Cooperative Oncology Group (ECOG) performance status 0) were treated with a daily dose of 800 mg imatinib planned over 2 years. The progression arrest rate after 6 months of imatinib treatment (PAR_{6mo}) was the primary end-point. Patients showing disease progression under imatinib could be treated with nilotinib 800 mg daily. Accrual started in July 2010 in four GISG centres and finalised in September 2013.

Results: The final analysis for the primary end-point in the evaluable patients of the full analysis set revealed a PAR_{6mo} of 65%. Subsequent progression arrest rates at 9, 12, 15, 18, 21 and 24 months were 65%, 59%, 53%, 53%, 50% and 45%, respectively. None of the patients died within the study observational period. Best reported response was seven partial responses at 21 months revealing an overall response rate of 19%. Eight patients treated with nilotinib demonstrated a PAR at 3 months of 88% (7/8); no more disease progressions occurred until end of study. In general imatinib adverse events were mild to moderate.

Conclusions: Imatinib induces sustained progression arrest in RECIST progressive desmoid tumour patients. In addition, nilotinib had the potential to stabilise desmoid tumour growth after treatment failure with imatinib.

1. Introduction

Desmoid tumours are rare monoclonal, fibroblastic proliferations characterised by an often unpredictable clinical course. Although histologically benign, desmoid tumours are locally invasive and associated with a high local recurrence rate, but lack any metastatic potential. According to the World Health Organization, they are defined as 'clonal fibroblastic proliferation that arises in the deep soft tissues and is characterised by infiltrative growth and a tendency toward local recurrence but an inability to metastasise' [1]. Considering the variable clinical presentations, anatomic locations and biological behaviours, an individualised treatment approach is required and different treatment recommendations and therapeutic algorithms have been developed recently [2,3]. The incidence is less than 3% of soft tissue tumours with a peak age of about 30 years [4]. Although most desmoid tumours occur sporadically, approximately 5–10% arises in the context of familial adenomatous polyposis (FAP). Sporadic ones predominantly affect young adults, especially females and sometimes related to pregnancy. Desmoid tumours often involve the extremities (including pelvic and shoulder girdles), the trunk (mostly abdominal wall), and the abdominal cavity (mostly within the mesentery or the pelvis) and the head and neck.

No evidence-based approach for the treatment of this disease is available as of today [3]. A careful counselling at a reference centre is mandatory and should be offered to all patients affected by sporadic desmoids from the time of their diagnosis. It is reasonable to consider watchful waiting as an initial step before undertaking subsequent treatments [5]. Surgery with or without radiotherapy is one therapeutic option for progressing patients, except if mutilating and associated with considerable function loss [6]. The Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer identified moderate dose radiotherapy as an effective treatment option for desmoid tumour patients with slow responses after radiation and continuing regressions documented even after 3 years [7]. Different systemic treatment approaches have been investigated for advanced disease [8] and promising prospective but uncontrolled data could be demonstrated using the tyrosine kinase inhibitor imatinib.

The initial data on the use of imatinib in desmoid tumours were generated by Mace *et al.* who observed a response in 2 patients with extra-abdominal aggressive fibromatosis [9]. In contrast to other imatinib responsive tumours, no genomic changes of *KIT* have been observed in desmoids showing that the response to imatinib is not attributable to *KIT* alteration [10]. Despite a rather low response rate ranging from 5 to 15%, high rates of stabilisation of around 60–80% with a favourable toxicity profile were documented in three prospective, non-randomised trials [11–13].

The objective of the present study of the German Interdisciplinary Sarcoma Group (GISG) was to evaluate the activity and safety of imatinib over a planned treatment period of 2 years in patients with Response Evaluation Criteria in Solid Tumours (RECIST)