PERGAMON

European Journal of Cancer 38 (2002) S138–S141

European Journal of Cancer

www.ejconline.com

The EORTC Soft Tissue and Bone Sarcoma Group

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Abstract

The EORTC Soft Tissue Sarcoma Group was founded 25 years ago and has since developed into one of the leading cooperative groups in the research of sarcomas and has members from 40 institutions from 13 countries. The activities of the group have primarily been within the areas of standards for local as well as systemic treatment strategies, new drug development and quality control procedures. The group has a extensive quality control programme involving a strict membership policy, central review of the responses, central review of pathology, use a systemic therapy check-list and on-site monitoring of studies. A large database with over 2500 patients included in EORTC STBSG chemotherapy trials has been developed. So far, the STBSG has conducted more than 40 clinical trials accruing more than 250 patients per year, some of which has been performed in collaboration with other prestigious groups.

Keywords: Soft-tissue sarcomas; Osteosarcoma

1. Introduction

The EORTC Soft Tissue and Bone Sarcoma Group was founded in September 1976 during a meeting held in Zurich where G. Bonadonna (Italy) was elected chairman and H.M. Pinedo (The Netherlands) became secretary and study co-ordinator of the first study (62761). Other founding members came from France, Germany, Belgium, Switzerland, UK and The Netherlands. The objectives of the group were to develop, stimulate and co-ordinate studies on all aspects of the treatment of sarcomas within the framework of the EORTC. The second objective was to organise congresses, symposia and conferences to promote these studies.

In 1978, the Soft Tissue Sarcoma Group merged with the International Osteosarcoma Working Party to form the EORTC Soft Tissue and Bone Sarcoma Group (STBSG). The activities of the group have primarily been within the areas of standards for local, as well as systemic, treatment strategies and new drugs development. Next to the study of new agents, the Group has developed very strict quality control procedures and played a major role in the development of the RECIST criteria.

The quality assurance programme involves a strict membership policy, central review of responses, central review of pathology, mandatory use of a systemic therapy check-list and on site monitoring visit. In 1995–1996, the Group participated in the EORTC Quality Control Programme; the results showed a major improvement in data quality when a Systemic Therapy Checklist is used as an integral part of the hospital file for data recording in multicentre multinational trials [1].

Soft-tissue sarcomas are rare tumours. Their annual incidence is around 2–3/100 000. There are multiple histological subtypes grouped under the heading of soft-tissue sarcomas for the purpose of treatment, although an increasing number of new treatment options are expected to be directed more specifically at individual histological subtypes. Local surgery, combined with adjuvant radiotherapy, whenever feasible, is usually the first-line of management. The addition of postoperative radiotherapy appears to reduce the rate of local recurrence significantly [2]. However, even an optimal local treatment does not prevent the occurrence of distant metastases in more than 50% of the patients—especially those with high-grade tumours.

Although the effect of adjuvant chemotherapy has been studied by several groups, the results do not allow any final conclusions. A recent international meta-analysis in which the STBSG was one of the major participants, indicated an effect on progression-free survival,

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0959-8049/02/$ - see front matter
PII: S0959-8049(01)00444-0

but no effect on overall survival [3]. Chemotherapy is widely used in the treatment of advanced disease, basically with a palliative intent, as most initially chemosensitive patients recur presenting highly chemoresistant disease.

The STBSG has been one of the major international groups studying the diagnosis and treatment of sarcomas. In the present paper, the principal achievements of the group will be summarised.

2. Principal achievements

2.1. Studies on neo-adjuvant and adjuvant chemotherapy

The Group has conducted the only prospective randomised trial (62874) comparing neo-adjuvant chemotherapy versus no chemotherapy in 150 patients with operable tumours [4]. It showed that chemotherapy did not interfere with planned surgery and did not affect postoperative wound healing. Although not powered to draw definitive conclusions on benefit, the results did not suggest major survival benefits with neo-adjuvant chemotherapy.

The EORTC study 62771 is the largest (468 patients) prospective randomised study comparing adjuvant chemotherapy versus no adjuvant chemotherapy to date. The results showed an advantage of adjuvant treatment with cyclophosphamide, vincristine, doxorubicin and dacarbazine only in delaying local recurrences for patients with localisation other than limbs [5]. This trial was also a major contributor to the international meta-analysis of adjuvant chemotherapy in soft-tissue sarcomas [3]. A study testing adjuvant chemotherapy with high-dose doxorubicin, ifosfamide and lenograstim in high grade soft-tissue sarcomas is ongoing (62931). After the publication of the meta-analysis, the role of adjuvant chemotherapy is still very important, and this is probably the last study trying to solve this question.

2.2. Phase III studies in advanced soft-tissue sarcomas in first-line chemotherapy

The study 62761 (1976–1980) compared in 312 patients two schedules of combination chemotherapy with cyclophosphamide, vincristine, doxorubicin and DTIC, the so-called CYDADIC regimen. The study pointed out the essential role of doxorubicin that has to be administrated at an interval of no longer than 4 weeks [6].

The study 62851 (1985–1990) compared in 729 patients doxorubicin versus the doxorubicin + ifosfamide versus the CYDADIC regimen. No statistically significant difference was detected among the three study arms in terms of response rate, remission duration or overall survival [7].

In studies 62801 and 62901, in which 210 and 334 patients were randomised, respectively, doxorubicin, the standard arm, was compared with two schedules of high-dose epirubicin. Both studies showed no superiority in the experimental arms. There was no difference in overall and progression-free survival, as well as in the response rate. Both dose schedules of epirubicin were more myelotoxic than doxorubicin. It was concluded that, when studied in a large randomised study, epirubicin is not a preferred alternative to standard-dose doxorubicin in the treatment of patients with advanced soft-tissue sarcomas [8,9].

The study 62903 (1992–1995) compared in 314 patients a standard-dose regimen containing doxorubicin (50 mg/m^2 on day 1) and ifosfamide (5 g/m^2 on day 1), or an intensified regimen, combining doxorubicin (75 mg/m^2 on day 1), the same ifosfamide dose, and recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF; sargramostim, 250 μg/m^2 on days 3–16); all courses were repeated every 3 weeks. The use of rhGM-CSF allowed safe escalation of the chemotherapy doses. Despite a 50% increase of the doxorubicin dose intensity, the high-dose regimen failed to demonstrate any impact on survival [10].

The last phase III study 62971 as first-line treatment was opened in February 1998; 326 patients were randomised into three arms: (a) doxorubicin (75 mg/m^2 on day 1), (b) ifosfamide (3 g/m^2 days 1, 2, 3), (c) ifosfamide (9 g/m^2 3 days' infusion). As a consequence of a preliminary analysis showing no differences in response rate but higher toxicity in both ifosfamide arms, the study was prematurely closed in October 2001.

Based on these studies, the EORTC-STBSG has concluded that doxorubicin is the most active drug in the treatment of soft-tissue sarcomas, its therapeutic activity is not increased when it is administrated in combination therapy and it is still the standard chemotherapy against which new treatments should be compared.

2.3. Phase II studies in advanced soft-tissue sarcomas in first-line chemotherapy

From March 1980 to November 1980, 83 patients were randomised between doxorubicin (75 mg/m^2) and carminomycin (20 mg/m^2), both administered as an intravenous (i.v.) bolus every 3 weeks. The results showed that carminomycin was not active [11]. From May 1984 to January 1986, 203 patients were treated with doxorubicin (50 mg/m^2) followed by a 24-h infusion of ifosfamide (5 g/m^2) plus mesna (2.5 g/m^2) repeated every 3 weeks. The results showed that the regimen was active and myelosuppression was the dose-limiting toxicity [12].

From July 1989 to June 1990, 111 patients received doxorubicin (75 mg/m^2) plus ifosfamide (5 g/m^2) every 3 weeks for up to seven cycles. rhGM-CSF (250 μg/m^2)

was administered once or twice daily by subcutaneous (s.c.) injections for up to 14 days. Full protocol dose intensity of chemotherapy was administered to the majority of the patients. This high-dose regimen of chemotherapy was feasible under rhGM-CSF cover and produced a higher response rate and median survival than previously seen by the Group [13].

From June 1995 to April 1996, 86 patients were randomised to either docetaxel (100 mg/m^2/1-h i.v. infusion q 3 weeks) or doxorubicin (75 mg/m^2/bolus injection q 3 weeks). The response rate to doxorubicin therapy was 30%, whereas no responses to docetaxel were seen. Consequently, the trial was closed prematurely and no phase III study was conducted [14].

From May 1997 to June 1998, 95 patients were treated with either CAELYX (liposomal doxorubicin) (50 mg/m^2/1-h i.v. infusion q 4 weeks) or doxorubicin (75 mg/m^2/i.v. bolus q 3 weeks). CAELYX was significantly less myelosuppressive as only 6% had grade 3 and 4 neutropenia versus 77% on doxorubicin. The responses observed were the same with both agents [15]. A new phase I study was scheduled to open in November 2001 in order to investigate CAELYX in combination with ifosfamide.

From October 1982 to October 1984, ifosfamide (5 g/m^2) and its parent analogue cyclophosphamide (1.5 g/m^2) were studied in 171 patients in a randomised phase II study. A higher response rate with less myelosuppression suggests that ifosfamide may have advantages over cyclophosphamide in combination therapy [17,18]. From February 1992 to July 1996, 185 patients were randomised to receive either ifosfamide (5 g/m^2/day 24 h infusion q 3 weeks) or ifosfamide (3 g/m^2/day 4 h infusion/d1, 2, 3 q 3 weeks). The study showed a higher response rate when ifosfamide was administered in the 3 consecutive days.

2.4. Phase II studies in advanced soft-tissue sarcomas in second-line chemotherapy

The group has studied the activity of several new compounds in second-line treatments such as cisplatin, chlorozotocin, methotrexate, PALA, ellipticinium, mitomycin-C, etoposide, DTIC (high dose), TGU, MDS, mitozolomide, MZPES, ACNU, fotemustine, miltefosine, MT-PPE, docetaxel, etoposide oral, temozolomide, tomudex, gemcitabine and ET 743 of which only DTIC (high dose), docetaxel and ET 743 showed antitumoral activity.

2.5. Other studies

A prospective randomised study of chemotherapy combined with hyperthermia is currently underway in patients with locally advanced sarcomas. Another trial is testing the role radiotherapy in patients with aggressive fibromatosis. In addition, the EORTC STBSG participates in the EURO-EWING 99 study evaluating the optimal consolidating chemotherapy and especially the effect of HDCT. In parallel with this trial, the group is performing a 'window study' with weekly cisplatin plus oral etoposide in patients with bone and/or bone marrow metastases at presentation, a particularly poor prognostic group.

In collaboration with the European Osteosarcoma Intergroup (EOI) the STBSG has performed a number of studies. The study 80831 (1983–1986), a randomised pilot study assessing the tolerability and efficacy of two drug combinations in 307 patients with osteosarcomas (DOX/CDDP versus DOX/CDDP/high-dose MTX), showed that a brief, intensive chemotherapy regimen of DOX/CDDP produced excellent long-term results [16]. The study 80861 (1986–1993) compared in 407 patients a short, intensive chemotherapy regimen with doxorubicin and cisplatin with a complex and longer-duration drug regimens based on the T10 multidrug protocol. No difference in survival between the two arms was seen and, as the two-drug regimen is shorter in duration and better tolerated, it is therefore preferred [17].

The study 80862 (1986–1990) evaluated in 109 patients the efficacy of a combination of platinum, ifosfamide, and doxorubicin in the treatment of osteosarcoma. The activity of methotrexate [19], cisplatin [20], ifosfamide and iproplatin [21] were evaluated in osteosarcoma. In June 1993, the randomised study 80931 was initiated studying the effect of chemotherapy with or without granulocyte colony-stimulating factor in operable osteosarcoma (at present involving 470 patients).

More recently, the group has started to investigate the activity of new drugs on specific sarcoma subtypes such as gastrointestinal stromal sarcoma (GIST). In this tumour type, the group was involved in the development of the drug STI 571. From August to December 2000, the group performed a phase I study on STI 571 (40 patients). From December 2000 to April 2001, 51 patients with GIST were registered in the phase II study. Preliminary results strongly demonstrated that STI 571 is an active drug in GIST and, consequently, in January 2001 a phase III trial has started randomising between 400 and 800 mg (at present involving 750 patients). The results of the phase I trial were presented at the plenary section of the American Society of Clinical Oncologists (ASCO) 2001 meeting [22,23].

3. Concluding remarks

So far, the STBSG has conducted more than 40 clinical trials accruing more than 250 patients per year, some of which has been performed in collaboration with

other prestigious groups such as the South West Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), National Cancer Institute of Canada (NCIC), Australasian Gastro-Intestinal Trials Group (AGITG) and French, Italian and Scandinavian Sarcoma Group (FSG, ISG and SSG). A unique database with over 2500 patients has been developed. As a consequence of the above-described achievements, the STBSG is today considered one of the leading cooperative groups in the research of sarcomas with members from 40 institutions from 13 countries.

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