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Editorial

Etoposide for Soft Tissue Sarcomas: Fact or Fiction

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SOFT TISSUE sarcomas (STS) are rare diseases and in several aspects difficult to treat. Best results of surgery are usually obtained in centres having a specific expertise in soft tissue sarcomas, and the tumours are relatively radiotherapy- and chemotherapy-insensitive. In the present issue of the *European Journal of Cancer*, Saeter and associates (pp. 1551–1558) representing the Scandinavian Sarcoma Group, present a study with two interesting aspects: (1) the use of etoposide and (2) the attempt to remove remnant tumour metastases surgically following chemotherapy.

The potential of chemotherapy for soft tissue sarcomas is limited, due to the availability of only 2–3 active drugs [1]. Commonly, doxorubicin and ifosfamide are considered the most important drugs for the treatment of soft tissue sarcomas, and while DTIC also yields activity, unfortunately its activity is only very short-lived [2]. Etoposide is not commonly considered to be an active drug for STS, based on the results of limited phase II studies. However, in various tumour types the effect of etoposide has been shown to be largely schedule dependent, presumably related to the fact that etoposide mainly exerts its cytotoxic effect in the S and G2 phase of the cell cycle. Despite the relatively high bioavailability of oral etoposide, several studies exploring various etoposide schedules aiming for long-term exposure by oral administration had largely been negative [3–5]. In addition, a phase II study involving ifosfamide at a dose of 2.5 g/m^2 per day and intravenous etoposide by short-term infusion, at a dose of 100 mg/m^2/day, days 1–3, only yielded an objective tumour regression in 16% of 44 patients, which is clearly no better than the results achieved with ifosfamide alone [6]. In contrast, a very small phase II study using a similar dose of ifosfamide, combined with oral etoposide for 8 days at a dose of 50 mg/m^2, yielded a response rate of 38% [7]. Given the previously mentioned negative results of phase II studies with oral etoposide in this disease, the latter study is difficult to interpret. Either there was synergism, or there was an unintended patient selection. If synergism plays a role, the 16% response rate in the Mayo Clinic study [6] becomes difficult to explain. That study differs from the one of Saeter and associates [8] in etoposide dose and the way it was administered.

Initially, Saeter and associates piloted the combination of etoposide and ifosfamide in a single centre study. Etoposide was given at the relatively high dose of 600 mg/m^2 in a 72 h continuous infusion and ifosfamide at a dose of 1500 mg/m^2 per day for 3 days. A response rate of 40% was achieved. Thus, these three studies [6–8] leave us with uncertainties on three aspects concerning the role of etoposide for the treatment of soft tissue sarcomas: (a) dose, (b) schedule and (c) potential synergism with ifosfamide. All the studies also suffer from a limited size and (as mentioned) the potential of patient selection. To exclude an influence of patient selection, it is usually recommended to repeat such a single-centre experiment in a multicentre setting. The Scandinavian Sarcoma Group should be complimented with the fact that they actually did so. Interestingly, the multicentre experience appears to confirm the single-centre experience. However, the presently reported study (Saeter and associates) still leaves us with some uncertainties.

The authors indicate a response rate after excluding patients with liver metastases, which is not commonly done in other studies and despite their correct conclusion that patients with liver metastases generally do worse, it is dangerous to make any comparison based upon this particular response rate. Moreover, giving a response rate based upon an analysis of patients responding to chemotherapy plus those converted to response by additional surgery could be confusing. Therefore, the response rate of 39% based upon the intention to treat analysis is best for comparisons with other studies.

The authors correctly caution for overinterpretation of a potential dose–response relationship. In their own study, the margin between the etoposide dose achieved in patients progressing versus the etoposide dose achieved in patients responding is only 8%. Moreover, with a 50% lower dose, Edmondson and associates only achieved a response rate of 16% [6]. The latter would support a dose–response relationship, while the former hardly supports the existence of a wide therapeutic margin. It is also of particular concern that the time to progression in responding patients was no different from other studies in soft tissue sarcomas [10]. In a similar multicentre setting using high-dose doxorubicin

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plus standard-dose ifosfamide, the EORTC Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) initially achieved a 45% response rate in a large phase II study involving over 100 patients [9]. The time to progression in the EORTC study is similar to the Scandinavian experience. Although there is no proper explanation, it is of concern that the EORTC STBSG subsequently could not confirm this high response rate in a randomised study comparing the aforementioned regimen with a standard dose regimen of doxorubicin and ifosfamide [11]. One suggestion may again be that in the phase II study, a stricter selection of patients is applied by investigators within the margins given in the inclusion and exclusion criteria of the study protocol. Also, one has to consider the experience obtained by both SWOG and EORTC with subsequent studies involving doxorubicin plus DTIC and doxorubicin plus ifosfamide, respectively [10]. Over the years, both groups have seen a gradual decrease in the response rate obtained with the regimens without changing dose, interval or dose reduction schedules. A proposed explanation for this change over time relates to the sophisticated and more detailed radiology techniques that have become available.

The second important issue of the Scandinavian study is the attempt to remove remnant lesions after chemotherapy by additional surgery. Over the last few years, various reports have indicated the importance of metastatectomy in the treatment of soft tissue sarcoma patients [12, 13]. In addition, the MD Anderson group published their experience of a large series of patients treated with the so-called CYVADIOC regimen [14]. They indicated that conversion of partial remission following chemotherapy to complete remission by additional surgery largely improved the survival of these patients. This experience is now confirmed by the Scandinavian study. A similar approach was also pursued by Casali and associates [15]. They studied epirubucin (a drug now known to have only limited activity in soft tissue sarcomas) with ifosfamide and DTIC in a highly selected group of patients with either locally advanced disease or a few pulmonary metastases, but still amenable to surgery. The response rate to presurgery chemotherapy was 49%, further highlighting the possible influence of patient selection on chemotherapy results. These three different observations suggest that for patients with metastatic disease, surgery may also play a major role in optimal treatment, aiming at prolonged disease-free survival. Since the precise role of adding chemotherapy to surgery in these patients is yet undefined; recently an intergroup study has been initiated comparing metastatectomy to metastatectomy plus chemotherapy. This study, co-ordinated by the EORTC with participation of the Scandinavian Sarcoma Group, the Swiss SAKK Group and the American Eastern Cooperative Oncology Group, will hopefully answer this important question in a large sample size.

Although the study presented by Saeter and associates, as indicated above, addresses important issues and yields very interesting results, the final answer to the question of the use of high-dose etoposide in the treatment of soft tissue sarcomas will have to come from an appropriately designed randomised study with a relatively large sample size. Such a study is awaited with interest.

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