Single-agent chemotherapy *versus* polychemotherapy in first-line treatment of advanced soft tissue sarcoma: for and against on the basis of the recent EORTC 62012 phase III trial

Interview with B. Kasper[1] *and* G. Grignani[2] *by* G.G. Baldi[3]

In favour of single-agent chemotherapy:
B. Kasper[1]
In favour of combination chemotherapy:
G. Grignani[2]

Introduction

Recently Ian Judson and colleagues, on behalf of the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG), reported in *The Lancet Oncology* the results of a randomised phase III study (EORTC 62012) that compared single agent chemotherapy with doxorubicin *versus* dose-intensive doxorubicin and ifosfamide in the first-line treatment of metastatic soft tissue sarcoma (STS) [1]. There was no significant difference in overall survival (OS), the primary endpoint of the study, between groups (median OS 12.8 months in the doxorubicin group *vs* 14.3 months in the doxorubicin and ifosfamide group; stratified log-rank test p=0.076), despite median progression-free survival (PFS) and overall response rates being significantly higher for the doxorubicin and ifosfamide group compared with the doxorubicin group (p=0.003 and p<0.0006, respectively). The authors conclude that these results do not support the use of intensified doxorubicin and ifosfamide for palliation of advanced STS, and that doxorubicin alone remains the standard treatment in Europe in this setting.

Despite these data, the question of whether combination therapy should be routinely used in the first-line setting is still open in the medical oncology sarcoma community. Thus, we interviewed two opinion leaders on this topic to try to clarify the role of combination therapy *versus* single-agent therapy in the first-line treatment of metastatic STS.

1. What is, in your opinion, the best "first-line" chemotherapy treatment for patients with advanced non-resectable soft tissue sarcoma?

Pro single-agent chemotherapy

As effective targeted treatments are not available for most advanced and/or metastatic STSs, doxorubicin and ifosfamide – which have been used for more than 30 years –remain the backbone of systemic chemotherapy. In most cases, patients with advanced soft tissue sarcomas have a poor prognosis and the primary goal of treatment is disease control and palliation. Therefore, in my view, doxorubicin alone remains the standard of care in the first-line treatment of advanced and/or metastatic STS patients.

Pro combination chemotherapy

In recent years, the field of STS has passed through an unquestionable expansion of biological knowledge that has increased our ability to discriminate entities that were formerly unrecognized. Gastrointestinal stromal tumour is the best example [2]. This better classification has had two consequences: STSs are less commonly gathered as a single entity, and, secondly, different therapies are increasingly recognized as more appropriate to specific histotypes [3]. For instance, ifosfamide or taxanes are thought to be more active in synovial sarcoma and angiosarcoma, respectively [4, 5]. Unfortunately, in rare tumours such as STS, it has not been possible yet to translate the newer insights into clinical trials so as to generate the necessary scientific evidence. In this scenario, the issue of polichemotherapy *versus* monochemotherapy has to be put into context of each single patient, in a strategy shared, as much as possible, with him/her, bearing in mind that there is a small proportion of patients who may become long survivors [6, 7] regardless of their metastatic disease. Having said that, in the literature there is some evidence supporting a potential benefit of combination therapy [1, 8]. Therefore, the therapeutic decision needs to take into account several aspects related to the disease (histotype, presentation,

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foreseeable conversion to resectability) and to the patient (Performance Status and decision). Based on this premise, a treatment with doxorubicin plus either ifosfamide or dacarbazine [9] may be proposed especially to relieve symptoms or to pursue surgical conversion.

2. What do you think about the role of single-agent chemotherapy *versus* polychemotherapy in the advanced setting, considering available data, especially the recent published EORTC 62012 phase III trial?

Pro single-agent chemotherapy

The question of whether doxorubicin alone or the combination of doxorubicin and ifosfamide should be used routinely in the first-line setting has always been controversial. Until now, all existing published literature – randomized trials and even meta-analyses – were not able to demonstrate any improvement in OS by combination therapies or dose intensification [9-12]. Most recently, the EORTC STBSG published data on the EORTC 62012 phase III trial, which addressed this question [1]. In this study, doxorubicin 75 mg/m² was given either as single-agent or intensified doxorubicin (75 mg/m²; 25 mg/m² per day, days 1-3) plus ifosfamide (10 g/m² over 4 days) was administered as first-line treatment. Although both doxorubicin and ifosfamide doses were higher than those reported in previous trials, the EORTC trial failed to show an improvement in OS (12.8 months *vs* 14.3 months; p=0.076). However, it demonstrated an almost doubling in response rate (14% *vs* 26%; p<0.0006) and prolonged PFS for the combination *versus* monotherapy. The decision of monotherapy or polychemotherapy should be clearly guided by the treatment goal in individual patient's situation. If the primary goal of therapy is disease control and palliation, doxorubicin monotherapy remains the standard of care and is the appropriate treatment option with lower toxicity. Conversely, combination treatment would be justified if tumour shrinkage is important, e.g. to relieve acute symptoms or in the neoadjuvant setting before surgery or radiotherapy.

Pro combination chemotherapy

The unsatisfactory survival and response rate with doxorubicin chemotherapy has been the most powerful boost in the search for drugs for almost 30 years, in an effort to improve these middling results. The last EORTC study has formally shown evidence of superiority in terms of objective response and PFS in favour of the combination, albeit at the price of reversible increased toxicity. The primary objective of the study, i.e. OS, was superior in the combination arm, but did not achieve statistical significance. In the enlightening editorial [13] commenting on these results, it was clearly pointed out how slightly different statistical assumptions would have made the OS result not only clinically but also statistically significant. Moreover, although at present we remain without prospective evidence, few sarcoma experts would suggest an ifosfamide-based therapy in leiomyosarcoma that represented 26% of enrolled patients [14]. These results give clinicians the opportunity for the above-mentioned individualized decision making, in an attempt to maximize efficacy for each patient.

3. The EORTC 62012 phase III trial showed a benefit in terms of progression-free survival (PFS), but not overall survival (OS), the primary endpoint of the study. What do you think about the choice of this endpoint? Do you think this is a correct endpoint for a trial in metastatic disease in soft tissue sarcoma?

Pro single-agent chemotherapy

The EORTC 62012 study failed to show a benefit in terms of OS, the primary endpoint of the trial. However, PFS was significantly prolonged by about 3 months – 4.6 months for the doxorubicin alone group to 7.4 months for the intensified doxorubicin plus ifosfamide group (p=0.003). Nevertheless, OS still remains a meaningful endpoint and a key goal of treatment especially in the first-line situation. In the palliative setting, however, disease control can delay deterioration of tumour-associated clinical symptoms and, in this case, prolonging disease progression for as long as possible might be the priority. In these situations, PFS could be equally important as OS and should preferably be chosen as primary endpoint. One prominent example for this strategy is in the recently published EORTC/STBSG PALETTE trial evaluating pazopanib *versus* placebo in the advanced setting; data showed a PFS advantage of about 3 months with pazopanib, leading to approval of this drug in several STS subtypes [15], even though there was no advantage in terms of OS.

Pro combination chemotherapy

OS is the gold standard because of its unquestionable relevance and reproducibility. Unfortunately, despite of its simplicity, nowadays, it is strongly affected by the availability of several lines of therapy, each one of them potentially affecting the duration of life. The assumption that the probability of having access to these drugs is evenly distributed among patients participating in a former randomized trial, is in my opinion quite weak. For example, both the

PALETTE or EISAI studies [15, 16] did not allow crossover and both of them involved patients who could have been previously treated in the EORTC study. We are in need of validated surrogate endpoints to overcome the limitations of OS. While awaiting these innovative endpoints, in the metastatic setting, I would consider PFS to be a more appropriate endpoint, especially in the context of first-line trials after which patients have a high probability of receiving several further lines of treatment that jeopardize a clear interpretation of OS.

4. The benefit in terms of progression-free survival (PFS) in the EORTC trial was about 3 months. Do you think that a subset of patients might derive a larger benefit and so also obtain an overall survival (OS) advantage?

Pro single-agent chemotherapy

The only conclusions which can be drawn from the published data of the EORTC 62012 trial are that the effects of treatment in terms of PFS differed between certain subgroups of patients. Those with high-grade tumours and worse Performance Status benefited more from combination treatment than did others. A greater benefit with combination treatment could also be demonstrated for patients aged 40-49 years. However, no further conclusions could be drawn from this regarding OS.

Pro combination chemotherapy

To look for results beyond pre-specified subsets of patients is a useful exercise to generate hypotheses that have to be prospectively confirmed. Having said that, I think the study suggests that the beneficial effect of combination chemotherapy is likely distributed along a gradient, in which age, tumour grading and symptoms are key components of increased advantage. I presume that interesting information could be generated by analysing the data set regarding the impact of histology or conversion to surgical resectability.

5. Considering the emerging data about the efficacy of histology-driven chemotherapy in advanced soft tissue sarcoma, do you think that the inclusion of patients with different histotypes in this trial treated with the samechemotherapy regimen might have had an impact on the final results?

Pro single-agent chemotherapy

Although no definitive conclusions could be drawn from the published data regarding different histologies, it is obvious that "lumping" together very different histological subtypes with very different characteristics in one trial is definitely not an optimal strategy. Recently, histological diagnosis is being used more and more to guide treatment for certain STS subtypes, e.g. taxanes for angiosarcoma or gemcitabine-containing regimens for leiomyosarcoma and undifferentiated pleomorphic sarcoma. It is well known that certain subtypes such as synovial sarcoma are quite chemosensitive. Those patients are often given combination treatment electively. Nevertheless, the proportion of patients with synovial sarcoma in the EORTC 62012 trial was quite high, suggesting that such a bias did not play a major role.

Pro combination chemotherapy

When the EORTC trial began, several pieces of information that we have now were not available. This concept was clearly stated in a nice presentation by Le Cesne at the 2008 ASCO Annual Meeting [17] regarding the same issue in the adjuvant setting, i.e. we should no longer design trials with STS as a single entity. With the hindsight of 10 years of scientific advances, the next generation trials will have to take into account the selective sensitivity of a given histotype to different combinations or drugs. This approach has been extremely rewarding in the field of malignant lymphomas [18] and in advanced STS, as seen in the PALETTE study [15].

6. In your referral centre, how do you select patients for mono- *versus* polychemotherapy?

Pro single-agent chemotherapy

As stated above, the primary goal of treatment should guide the treatment decision. In our sarcoma Unit, the gold standard for patients with advanced and/or metastatic STS in the palliative setting remains single-agent doxorubicin with its advantages of being able to be administered on an outpatient basis and its lower toxicity compared with combination chemotherapy. However, for younger patients with good Performance Status and without relevant comorbidities, we consider combination therapy if tumour shrinkage, relieve of symptoms or another intervention after response in form of a secondary curative intervention are anticipated. The final decision, of course, is usually discussed within a multidisciplinary team. Taken together, the findings of the EORTC 62012 study have helped us to individualise the care of our patients with this disease.

Pro combination chemotherapy

In principle, treatment is defined by our sarcoma board and based on the clinical description of the physician in charge of that specific patient. This permits a thorough discussion of the case based on information regarding Performance Status, the patient's willingness/desires, foreseen surgery eligibility and so on. Whenever feasible, we propose that the patient enters a clinical trial. In general, however, younger and symptomatic patients are invited to accept more aggressive treatment encompassing combination chemotherapies such as doxorubicin and either ifosfamide or dacarbazine according to their histotype. There are histotypes in which we do not propose combination chemotherapy, e.g. solitary fibrous tumour [19].

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