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Editorial Comment

Osteosarcoma: Time to move on?

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Osteosarcoma treatment follows very simple rules: if you want a cure, cut out all detectable tumour and poison invisible tumour cells with as much chemotherapy as the patient can tolerate. In this age of translational research and molecularly targeted therapies, such an archaic approach may seem anachronistic. However, in contrast to any subsequent development, the combination of multidrug chemotherapy and surgery has a strong history of being highly effective: long-term survival is being achieved in some two thirds of patients with localised extremity primaries and a quarter to a third of patients with axial primaries or primary metastases.[1–4] Leave out chemotherapy, and very few patients will be able to escape metastatic recurrence.[5] Leave out surgery, and local failure is almost inevitable.[6]

Against this background, recent years have witnessed considerable progress in imaging, revolutionised by magnetic resonance techniques, and supportive care. Maybe most importantly, there has been a major shift away from mutilating amputations. Limb-salvage surgery, which used to be reserved for few and particularly favourable situations, has now become the treatment of choice for most patients in most situations.[4,7] Innovative endoprosthetic devices allow the reconstruction of extremity defects even in young children who can retain considerable growth potential.[8,9] Radiotherapy may play a role in selected situations not amenable to surgery.[10,11]

In contrast to the advances achieved in local therapy, the past decades have seen very little change as far as systemic treatment is concerned. Most patients today are still receiving exactly the same drugs as they would have 25 or more years ago, namely doxorubicin, cisplatin, high-dose methotrexate, and sometimes ifosfamide, in varying combinations.[12,13] Nevertheless, even after a quarter century of experience with these four standard agents, some basic questions remain as unanswered as they were a generation ago. This includes the question which of the 'standard' drugs combined at which dosages would result in an 'ideal' combination and of course the question whether postoperative treatment alterations might help to improve the poor prognosis of patients with unfavourable histological tumour response to preoperative induction chemotherapy. Attempts to improve outcomes by combining the standard drugs at maximally tolerated doses or by increasing their dose intensity have not been met with success.[7,14] Considering this stagnation, it cannot come as much of a surprise that survival expectancies in Europe as well as in North America have also improved very little, if any at all, over the past 25 years.[15,16] Unless spectacular new therapeutic opportunities arise – and, despite all research efforts, these do not seem to wait around the corner – optimisation of therapies will have to be addressed in relatively large randomised trials. Given the low incidence of osteosarcoma and statistical constraints, such pivotal trials

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could in most instances not be performed by any one institution, country, or even multinational group alone, but require multicentric, multinational, intergroup collaboration. The current European and American EURAMOS study is the largest example of a successful intergroup endeavour. Open since 2005, it has already recruited over 1600 patients from over 300 institutions in 15 countries, approximately half of them from Europe.[17]

The TV meteorologist played by Bill Murray in the 1993 movie *Groundhog Day* finds himself stuck in a time loop, forced to relive the same day over and over and over again. Oncologists treating osteosarcoma have been stuck in a similar time loop for the better part of three decades, forced to relive the same tedious discussions about doxorubicin, high-dose methotrexate, cisplatin, and ifosfamide for year after year after year, lamenting again and again about being limited to less than a handful of effective agents and not even knowing how best to use them. Come 2010, oncologists around Europe find themselves facing a very different challenge, namely deciding if and how to incorporate a newly licensed drug into their standard repertoire. Like it or not, any discussion on osteosarcoma these days will soon revolve around this topic, and any editorialist, including this one, will find himself unable not to address it at considerable length. The drug under discussion is liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE, mifamurtide), a synthetic analogue of a component of the *Mycobacterium* sp. cell wall, probably acting through immunomodulation via activation of macrophages and monocytes.[18] This proposed mode of action also explains the spectrum of side effects, amongst which chills (89%), fever (85%), and fatigue (53%) are the most common.[19] Following a positive opinion by the EMEA's Committee for Medicinal Products for Human Use (CHMP), the European Commission granted centralised marketing authorisation for the treatment of non-metastatic, resectable osteosarcoma in March 2009, allowing the drug to be marketed in the 27 European Union member states, Norway, Iceland, and Liechtenstein.[20] The small enterprise behind the marketing application – thereafter quickly acquired by a large global pharmaceutical company[21] – heralded its availability as a 'significant milestone for physicians and patients in Europe'.[20] Given the potential economic implications, this jubilation should come as no particular surprise: In Germany, L-MTP-PE was announced to be marketed at €3223 incl. VAT per vial, amounting to €154,700 for a complete treatment course of 48 doses.[22] With approximately 500 million residents in the European Union and an estimated annual incidence of osteosarcoma of 3/million, some 1500 new cases per year can be expected in the 27 member countries, of which approximately 1000 will fall into the non-metastatic, resectable category for which the drug has been licensed. Treating 1000 patients with the drug at over €3000 per vial × 48 would therefore draw approximately €150 million from the European health care budget – and that is for the drug alone, not allowing for the additional costs associated with 48 intravenous infusions.

The European marketing authorisation resulted from a large, randomised phase III intergroup trial jointly performed in the United States by the Childrens' Oncology Group and the Pediatric Oncology Group (CCG/POG-INT033),[23,24] which evaluated the addition of L-MTP-PE to chemotherapy. Any interpretation of the trial's results, however, is not quite as straightforward as one might like. The rather complex factorial trial design with two potentially interacting randomisations, methotrexate/doxorubicin/cisplatin ± ifosfamide ± L-MTP-PE, resulted in a total of four treatment arms. Complicating matters even further, ifosfamide was *substituted* for cisplatin preoperatively and *added* to cisplatin only postoperatively.[23,24]

Factorial designs can work if there is no interaction between randomisations. A first published analysis of INT033, however, detected an interaction between its two randomisations, which basically destroyed the statistical assumptions on which sample size calculations had been based. No significant effect of L-MTP-PE on event-free survival was evident.[23] Subsequent re-analyses came to results that were more favourable for the drug.[24–26] The most recently published reanalysis of the non-metastatic cohort of the study reported improved overall survival ($p = 0.03$) and a trend toward improved event-free survival ($p = 0.08$) with L-MTP-PE. Very importantly for the interpretation of the results, the statistical interaction with the ifosfamide randomisation was now assessed as being no longer present – the p-values for interaction were 0.102 for event-free survival and 0.60 for overall survival, the significance cutoff had been set at 0.10.[24] A closer look at the published Kaplan–Meier curves, however, suggests that – even in the absence of statistical proof of interaction – any prognostic differences attributable to L-MTP-PE seem to have been more or less limited to patients who also received ifosfamide. As an example, event-free survival expectancies at 6 years for patients who had received chemotherapy without ifosfamide were 63% with and 64% without additional L-MTP-PE,[24] hardly a very convincing argument for the widespread adoption of the drug. Letters to the editor of the *Journal of Clinical Oncology* voiced interaction concerns and, while conceding that L-MTP-PE might possibly work with (or possibly even without) concurrent ifosfamide, agreed that the results of INT033 were far from being decisive and did not merit practice-changing conclusions.[27,28] EM(E)A's US counterpart, the FDA, seems to share such reservations and refused to grant a US marketing authorisation, stating that 'the FDA finds that there is not sufficient evidence of a survival advantage for the addition of MTP-PE to the standard chemotherapeutic regimen'.[29]

In my view, the current discussion on osteosarcoma raises some more general questions: In rare, 'orphan' diseases, how much proof should we require before accepting a new treatment as part of standard therapy? Should we be content with a narrower body of evidence than would be required for other, more common diseases? Are we bad physicians if we do not offer a particular innovation to our patients, even though there is a only a possibility that it might work under some circumstances? Or, are we bad physicians if we subject our patients and health care systems to the additional burdens associated with therapies that have not been evaluated nearly as thoroughly as one would like? In the case of L-MTP-PE, neither of the two options, neither simply ignoring the new drug with its possible potential nor its uncritical use at a rather preliminary stage of development, appears to be the appropriate choice. Confirmatory trials are undoubtedly desirable to

determine if the addition of this particular agent to chemotherapy is truly beneficial and, if so, if it is active in all patients or only in specific subgroups or with particular chemotherapy combinations. If well-designed trials produced positive results, skeptics like myself could finally be convinced that there is indeed more to treating osteosarcoma than combining good surgery with old-school, full force chemotherapy. Intelligent study designs incorporating biology-driven laboratory research should at the same time be allowed to define those circumstances in which the agent is most likely to be effective. If, however, well-designed trials failed to demonstrate any benefit of adding the drug to an already very demanding therapy regimen, which they might do just as well, scores of future osteosarcoma patients would be protected from an expensive, tedious, cumbersome, and yet ineffective treatment measure. There are, of course, many obstacles ahead if such trials are to be conducted, and overcoming these would require almost global cooperation in a complex, non-pharmaceutically funded setting. Similar challenges, however, have been overcome in the past[17] and should not deter investigators from trying to accurately define the value of new interventions.

The leading character in the movie *Groundhog Day* finally escapes his time loop after re-examining his life and priorities. Maybe those of us treating osteosarcoma can do likewise by re-examining why we have been stuck in the doxorubicin–methotrexate–cisplatin–ifosfamide loop for so very long and yet still do not know how best to use these four, far from having made any relevant progress overall. We might now have the chance to escape and to address new, biology-driven, future-oriented questions. Let us make sure that we do it right this time, that we perform the right studies early on, and that we define the exact role of new treatment modalities before using them indiscriminately. Otherwise, we will find ourselves stuck in yet another time loop of frustrating, never-ending, fruitless discussions. It is time to move on.

Conflict of interest statement

Consultant: IDM, Roche Pharma, Takeda Millennium Pharmaceuticals. Advisory Board Membership: Merck & Co.

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