Chemoradiotherapy of head and neck cancer – Can the bumble bee fly?
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It has been said that if a bumble bee knew anything about aerodynamics it would never dare to try to fly because the small wings would not be able to support the large clumsy body. In a similar fashion, one would expect that no oncologist would dare to introduce concurring chemoradiotherapy because abundant pre-clinical data indicated the lack of expected therapeutic benefits and so did early clinical experiences. Thus textbook chapters and review papers contained warnings against this interaction such as “Most of the large randomized trials have demonstrated no benefit from the use of radiation and chemotherapy”…; “there are no convincing data to mandate routine combined use of radiotherapy and chemotherapy”…[1]; “The evidence … is therefore that concurrent treatment is bad” [2]. Nevertheless, several investigators embarked on advanced clinical testing in randomised trials which have ultimately resulted in a vast amount of data which are presented in an updated meta-analysis with more than 17,000 patients included in randomized clinical trials [3].

This updated MACH-NC meta-analysis is now presented in this issue of the journal [3], and the initiators and key persons of this activity, Jean-Pierre Pignon and Jean Bourhis deserve admiration and credit for their initiatives and ability to perform these important meta-analyses in collaboration with investigators world wide. The current analysis, which deals with chemoradiotherapy of head and neck cancer, is thus the latest in a series dealing not only with meta-analyses of this sort presented here represent the level 1A evidence and will, therefore, serve as a guidance as to how to treat patients in the most efficient way. So what does the updated analysis then show? Nothing new – but more confirmed knowledge about what we have already learned. Concomitant chemoradiotherapy is likely to give a highly significant, although small, improvement in the survival of patients with squamous cell carcinoma of the head and neck. This is most pronounced if Cisplatin is included as the main drug and is especially seen in younger and fit patients. Drug treatment given before radiotherapy (induction or neoadjuvant) or after (adjuvant) does not yield a similar benefit, and it is likely to assume that it is the interaction with irradiation in the form of chemoradiosensitisation, which is the most likely contributor to this outcome. This is also supported by the fact that the total dose of the drugs is rather limited.

One may argue that the fact that a small reduction in distant metastases is seen with induction chemotherapy may indicate a function of the drug itself. That a similar reduction is not observed with concomitant treatment is probably due to variation in patient cohorts and details related to the drugs used, rather than a methodological difference, since it is intuitively difficult not to expect the same benefit on distant metastases irrespectively of how the drug is given in relation to radiotherapy, provided the same efficacy of the drugs exist.

A meta-analysis is the prime source of generating evidence but it also suffers from the problems that you can only ask a fairly simple question, such as: is the overall benefit improved? – but not: at what expense of acute and late morbidity? [2,7]. The problem with chemoradiotherapy in head and neck cancer is that the schedules are often rather toxic and associated with a substantial morbidity which in turn influences the compliance with treatment [8,9]. What does not come out of the analysis is the substantially enhanced morbidity seen during and immediately after treatment in many of the studies. Obviously this morbidity is to some extent outnumbered by the benefit of the combined treatment, resulting in an improved survival; but we must not forget that many patients do not comply with treatment, and patients who do not fulfil a planned course of radiotherapy due to morbidity with the interacting drug, are in fact in a worse situation than the ones who are treated with radiotherapy alone. This may well explain why elderly patients do not show a benefit, probably because these are not only elderly but also more fragile and with more co-morbidity, which makes the compliance with treatment worse [3]. The traditional head and neck cancer patients have more co-morbidity than most other cancer groups due to the often long-term use of tobacco and excessive alcohol consumption, and the co-morbidity associated with excessive use of tobacco and alcohol is often so severe that it influences the compliance with treatment [10]. It is, therefore, typical that many patients do not fulfill the full or planned course of chemoradiotherapy and especially in schedules using three cycles of 100 mg Cisplatin have problems with compliance being a significant issue. In fact, many institutions worldwide are not using that schedule despite its obvious contribution to generating the improved benefit [8,11,12]. It is “FDA approved”. That label is placed on many trials and especially on the study by Adelstein et al. [11] who introduced the 100 mg Cisplatin/m2 in the head and neck cancer treatment. And it has been haunting us ever since – not because it does not

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0167-8140/$ - see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.radonc.2009.06.001
yield the benefit as described in the original trial, but simply due to the very poor compliance [8]. New treatments, introduced frequently by the pharmaceutical industry, have normally used this “FDA approved” reference and it has been difficult to bring forward more acceptable schedules. The scenario has become even more confused since the other major side of squamous cell carcinoma where chemoradiotherapy has been introduced with benefits, namely the treatment of uterine cervical carcinoma, has done so mainly by using a different schedule, which has typically been 40 mg of Cisplatin given weekly [13]. That schedule has proven to have fewer problems with compliance and consequently it has currently taken a, constantly growing, larger place in the treatment of head and neck cancer where a weekly schedule with 40 mg Cisplatin in many places has become a dominating factor. We do, therefore, have the paradox that the treatment with chemoradiotherapy in head and neck cancer is argued with basis in the meta-analysis but is given with a schedule, which is not included or evident from the same meta-analysis.

A proper balance between information and evidence levels should in an ideal world include both the tumour response and the treatment-related morbidity, and the associated risk of not complying (and thereby failing the treatment). This is unfortunately not the case and we are therefore in the strange situation that we are recommending a treatment strategy which to a large cohort of patients is not acceptable, and where the community in general uses another schedule than what is recommended from the meta-analysis. What is really needed is a large comparative study between the two preferred chemoradiotherapy regimens, namely the one including Cisplatin with three cycles of 100 mg/m², and another with weekly courses of 40 mg/m². That will give us the final evidence of which would be the optimal schedule but that is probably not going to be so, because the view points in different institutions are so strong that if you favour one schedule you may disfavour the other one so much that you will not embark on a study.

How can we improve the effect of radiotherapy in head and neck cancer? Biologically there is strong evidence that the response, as in most other situations, follows a clear dose response relationship so any increase in dose is likely to result in better tumour control both in the primary T-site and in the nodes. This is the background for the use of hyperfractionation, which by use of multiple small doses per day allows a higher total dose to be given without increasing the risk of late effect (due to the difference in the alpha-beta ratio) [4,14]. The mechanism of chemoradiotherapy is most likely the same, namely a sensitisation of the radiation effect in such a way that the biological effect of the Gy becomes larger. Head and neck cancer does also contain hypoxic cells and hypoxic radioresistance is especially pronounced in this tumour type [15], a factor which has also been demonstrated in larger but more crude meta-analyses [16]. There are some pre-clinical indications that certain chemotherapeutic agents, such as Mitomycin C and Cisplatin may have a special effect on the hypoxic fraction in tumours and thereby not only secure enhancement of the dose but also to some extent be part of overcoming a potential hypoxic radio resistance [17]. This needs, however, to be convincingly proven in a clinical setting [18].

Another way to improve radiotherapy in squamous cell carcinomas of the head and neck is to avoid the radiation-induced repopulation by giving the treatment in a relatively short time by so-called accelerated fractionation [14]. Again, this has been subjected to a number of clinical trials and a large meta-analysis by the MARCH group [4,19], and again, there is a fairly uniform conclusion that moderate acceleration is beneficial, but probably only in the T-position and not in the neck nodes [19]. On the other hand, this sort of treatment can be given without any enhancement of late effects and only a minor increased acute reaction [19]. Although it may not benefit all patients [20,21], accelerated fractionation seems to be the treatment of choice as a base line radiotherapy schedule and has taken over as standard treatment instead of the more conventional five fractions of 2 Gy per week. More recently, however, all the hype have been focused on the use of EGFR inhibitors [12,22], and based on a single controlled clinical trial [23] the use of such treatment has been introduced and advocated, again by FDA and again in a situation where a more concerned and less enthusiastic introduction might have been beneficial. Rather than being the solution to improve head and neck cancer treatment for all patients, the combination with EGFR inhibitor suffers from the same problems as many of the other combined schedules: it has a heterogeneous outcome, which may be linked to radiotherapy schedule and tumour site; it has problems with the treatment of the elderly; and the morbidity is probably much more severe than that initially anticipated. There is no doubt that more clinical trials are needed to find the proper place for this treatment in head and neck cancer therapy. A single clinical trial is definitely not able to give the full answer to the role of this hopefully promising combined modality, especially when there are incing reports about unwanted morbidity [24–27].

In addition, the strategy for the therapy has deliberately been dramatically changed and IMRT has now become more the rule than the exception in treatment delivery, at least in more complicated cases. The picture of treating these patients has been changed and most recently it has become evident that if the etiological background for head and neck cancer is more complex with a rapid increase in the HPV-induced oropharyngeal tumours, which may have different responses and prognoses [28], which happily have improved and have thereby raised the questions as to whether the treatment strategy should be equally aggressive or whether one may reduce treatment burden (and risk of late morbidity) maybe by only relying on irradiation without additional concomitant drug treatment. Until this has been properly clarified, one should be a bit reluctant to use a different strategy in HPV-induced tumours among other reasons because it is unclear to which extent the result indicated in e.g. the meta-analyses are influenced by the results coming from patients with HPV-induced tumours and thereby this etiology has already influenced our outcome. Retrospective reanalysis and prospective stratification according to this parameter are highly warranted to clarify this very important point.

Finally, the introduction of new and potentially more efficient drugs, such as Taxanes is underway [12,29], and the renewed interest in induction chemotherapy [12] has been revitalised although there needs to be a strong case for doing so because of the substantial associated morbidity, and the fact that the benefit of acceleration is somehow in contradiction with the use of induction chemotherapy because it is probably not the overall treatment length variation alone but the total treatment time, which may influence the outcome. Thus there are indications that induction chemotherapy might have a benefit due to the drug itself but may in addition also cause repopulation and thereby there is a risk of losing on the roundabout what you have gained on the swing.

Taking all these things together, how then should we treat the advanced head and neck cancer? Well, if you surf the internet and look at the various databases you will reach the conclusion that the optimal treatment today would be to include the patient into a clinical trial with randomization to an EGFR inhibitor and where the treatment otherwise is composed of IMRT, chemoradiotherapy given with an accelerated hyperfractionated schedule and with the addition of a hypoxic radiosensitizer. Such treatment is evidence based and takes advance of the more recent progress within the field. The fact that the EGFR inhibitor is not fully included as an established modality, is partly because it, despite intense promotion and a lot of hype by the American authorities, is
still only based on the outcome of a single clinical trial where the data have been quite heterogeneous in different subgroups, and because it has a significant morbidity; and furthermore the interaction with EGFr inhibitors and other treatment modifying regimes (such as altered fractionation and chemoradiotherapy) is not yet clarified. All the above-mentioned activities can be justified, but some will have a substantial additional morbidity such as the chemoradiotherapy. In fact, the single most beneficial activity will probably be the use of hyperfractionation because it increased a higher dose, seems to have no resistance in either T or N position and can be given to all patients without increased late morbidity. Thus it represents probably the sole biological way to improve the therapeutic ratio in radiotherapy in head and neck cancer. Chemoradiotherapy may be a similar way to improve the benefit in both T- and N-sites, but at the expense of a substantial additional morbidity. However, it can be given without the extra radiotherapy resources required for the hyperfractionated schedules. It can also be applied together with accelerated treatment or combined schedules, but again with some risk of poor compliance.

Thus, chemoradiotherapy has been demonstrated to be effective although with limitations, which is linked to its morbidity. Despite the proven efficacy, we do not yet have a proper acceptable schedule and we are left with a hint of something which may be good, but also with a need to make it better. The use of weekly Cisplatin can be applied together with accelerated treatment or combined schedules, but again with some risk of poor compliance.

Yes, the bumble bee can fly but it happens in a clumsy and not in an efficient way and some adjustment is needed to help it do it more elegantly and a in less dangerous way.

Acknowledgement

Supported by grants from the Danish Cancer Society, The Danish Medical Research Council and Cirro, the Lundbeck Foundation Center for Interventional Research in Radiation Oncology.

References
