
Lobaplatin, a New Platinum Complex

For decades analogue research was a major source for new anticancer drugs. Some of today’s standard drugs are second or third generation analogues, doxorubicin and cyclophosphamide being prominent examples. In the context of the current public discussion about the cost/benefit ratio of new drugs analogue research has been occasionally criticized because the innovation potential is considered to be low in comparison to the development of new chemical entities (NCE’s). From the pharmaceutical industry’s viewpoint this lower innovation is generally balanced by a lower development risk. Preclinical models to characterize the toxicological and pharmacological profile of the analogue versus the mother compound are available and they even seem to have a certain predictivity for the clinical situation. Whereas with NCE’s the hope for completely new modes of action and thus new spectra of activity are the driving force behind the development, this is usually not the case with analogues. Therefore, the ultimate success of analogue development largely depends on the exact definitions of the development goals, and the stringency with which they are pursued.

Increasingly 'socio-economical' considerations will become part of the development strategy for new anticancer drugs. Health and Regulatory Authorities throughout the Western World have started to emphasize that the benefit of a new compound should be assessed not only in medical but also in economical terms. With analogues, for example, reduced toxicity in comparison to the parent drug may also diminish the need for expensive supportive care and this, in turn, can be expressed directly in units of money. But also non-monetary factors such as quality of life have to be carefully considered, when assessing the overall value of an analogue. In the light of the above, the question arises whether or not the development of a new, third generation platinum complex is still justified. I believe yes. The toxicological drawbacks of cisplatin are obvious and although the drug is comparatively cheap, supportive measures have become expensive. Although the second generation with carboplatin has solved some of the toxicological problems associated with cisplatin, there are suggestions that carboplatin may be less active than cisplatin, in particular in combination regimens [1, 2]. If the preclinical features of lobaplatin can be substantiated in clinical trials, this new platinum complex should have significant advantages over the presently available first and second generation platinum compounds. A toxicity profile which is similar to carboplatin combined with the high antitumor activity of cisplatin makes lobaplatin clinically attractive. In addition, lobaplatin did not show cross-resistance with cisplatin or carboplatin in a number of animal models.

First results from phase II studies carried out in Europe and in China indicate that lobaplatin may have significant activity in esophageal, refractory ovarian and non-platinum-pretreated small-cell lung cancer as well as in chronic myelogenous leukemia. To date more than 170 patients have been treated with lobaplatin, and the toxicity profile appears favorable: apart from bone marrow
suppression and mild nausea and vomiting, no other significant toxicities have been encountered. Whether or not lobaplatin ultimately fulfills the requirements defined in its project goals remains to be seen.

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Kaufmann M, et al.: Combination of grading and new biological factors (S-phase fraction and epidermal growth factor receptor) can predict relapse and survival in patients with node-negative primary breast cancer. Onkologie 1994;17:166-172.

Prognostic Factors in Axillary Node-Negative Breast Cancer

The understanding that breast cancer often represents a systemic disease has led to the concept of adjuvant therapy administered following surgical removal of the primary tumor. Thus, recurrence of disease and metastatic spread could be effectively postponed or prohibited by the administration of adjuvant therapeutic measures. It is not surprising, therefore, that the effectiveness of adjuvant therapy was first investigated in high-risk patients with positive axillary lymph node status constituting the most important prognostic parameter for the course of breast cancer. Further clinical studies have demonstrated, however, that the course of breast cancer could also be positively influenced by the administration of adjuvant therapy in patients with negative axillary lymph node status [1, 2]. It has to be stressed in this context that probably only a minor fraction of patients with breast cancer and negative axillary lymph node status who are characterized by their high-risk factor profile benefit from adjuvant therapy, whereas the others are being overtreated. Therefore, clinical investigators have been searching for a further and better definition of such risk factors which would determine the course of the disease. Thus, not only clinical factors but also markers of cellular proliferation and differentiation are being investigated for this purpose [3].

In the last issue of ONKOLOGIE Kaufmann et al. reported on the use of several such markers in predicting the course of patients with breast cancer and negative axillary lymph node status. In their analysis they have shown that disease-free survival (DFS) is negatively influenced by S-phase fraction and low concentrations of the progesterone receptor, whereas overall survival (OAS) is negatively influenced by S-phase fraction, epidermal growth factor receptor and histological grading. No influence was found to be exerted by DNA ploidy or the amplification of HER-2/neu oncogen upon the measured parameters. Finally, a combination of risk factors such as S-phase fraction and epidermic growth factor receptor were shown to have an even higher predictive potency than either factor alone. Extrapolating from their results, the authors have undertaken to define 3 different risk groups and – accordingly – advocated different therapeutic approaches. The approach and even more the latter conclusions are very exciting, and some of the data corroborate previous findings. However, in order to arrive at a definitive therapeutic consensus, conflicting data on the same topic will have to be carefully analyzed: Thus, e.g. the lack of the influence of the estrogen receptor upon either DFS or OAS is surprising [2], as is the lack of prognostic significance of the amplification of HER-2/neu oncogen [4]. Conflicting data with those presented in the study by Kaufmann et al. have also been reported about the correlation between estrogen receptor and the epidermal growth factor receptor [5]. Extrapolating from these examples, we have arrived at a point at which we understand that we should look for more clear-cut prognostic markers for the course of breast...
cancer with negative axillary lymph node involvement. Although the variables for which we could look are pretty defined, we are confronted with conflicting data about their prognostic significance concerning either DFS and/or OAS. Therefore, it has to be appreciated that Kaufmann et al. have produced results which take into account a combination of 2 or more prognostic factors such as S-phase fraction and epidermal growth factor receptor which seem to be of higher importance and to carry with them a pronounced risk for shortened OAS.

The question remains, however, how the problem of conflicting data about prognostic markers and the subsequent therapeutic approach concerning adjuvant treatment should be solved. One of the many possibilities would be a better analysis of prognostic indicators for the course of breast cancer with negative axillary lymph node involvement similar to the clinical analysis of the impact of adjuvant therapy performed by the Early Breast Cancer Trialists’ Collaborative Group [1]. Such a metaanalysis would allow us to arrive at conclusions based upon observations of many patients in a similar clinical situation. This would not only shed light on this very confusing matter, but also allow us to treat patients on a more individual basis. C. C. Zielinski, Wien

References

The report by Funke et al. indicates the problematic nature of phase II studies with cytokine combinations in renal cell cancer in regard to their clinical relevance. The authors used a reduced dose schedule of rIL-2 and rIFN-α without any objective response. It is important to present negative data of well-performed phase II studies, but it is an understatement if the authors conclude that no synergistic effects have been observed in a study without any response. In phase II studies using these cytokines as single agents or in combinations, the response rates vary between 0 and 35% depending on the schedule, dosage and patient selection [1]. The latter seems to be the most relevant factor for response induction and has to be taken into consideration in the conception of phase II studies and in the interpretation of their results [2, 3]. Indeed, a high proportion
of patients included into the reported study had unfavorable prognostic factors. Therefore, no final conclusions can be drawn concerning the (in)effectivity of this low-dosage schedule and a possible additive or synergistic effect of both cytokines in vivo. Other phase II trials with IL-2 and IFN-α have not yet confirmed a synergistic effect, too. In ongoing phase III trials no superiority was shown so far for the combination of both cytokines versus IL-2 alone in renal cell cancer [4].

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References

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