breast and colorectal cancer, the profile of oral chemotherapy is set to rise. Oral formulations of other cytotoxics, such as the taxanes, are also in development.

Potentially even more important in the future will be novel agents targeted to intra-cellular signalling pathways such as protein kinases. Several are being developed as oral therapies with imatinib and iressa leading the way. Imatinib, which inhibits the c-abl and c-kit tyrosine kinases, has excellent oral bioavailability and striking activity in CML and G.I. stromal tumours. Iressa is an oral anilinoquinazoline inhibitor of EGFR tyrosine kinase activity given once daily by mouth with activity in non-small cell lung cancer. Both iressa and tarceva (an oral quinazoline EGFR tyrosine kinase inhibitor also active in non-small cell lung cancer) cause a reversible acneiform rash. The same rash is seen with C225, the intravenously administered monoclonal antibody EGFR inhibitor emphasizing that route of administration alone will not avoid a "class effect" toxicity.

Although oral treatment is set to increase, concerns remain regarding compliance, absorption and variable pharmacokinetics as well as re-imbursement in some countries. The overwhelming majority of patients prefer oral chemotherapy (>80%) because of its greater convenience, avoidance of venepunctures and the greater sense of "control" over their treatment. Clinicians often question whether patients will take tablets reliably, but evidence for non-compliance is conflicting. Likewise, concerns over the consistency of bioavailability can often be overcome by improved formulation and drug delivery. There may also be an assumption amongst oncologists that i.v. administration is inherently more effective than oral treatment despite experience showing that in women with breast cancer responses are more durable with oral endocrine therapy than i.v. chemotherapy. Indeed, we must remember that anti-cancer drugs potentially toxic irrespective of the route of administration and must be carefully supervised by the oncology team. It is especially important to educate patients taking oral drugs, as well as their G.P., practice nurse and pharmacist, to recognise side-effects so that treatment can be interrupted where appropriate.

The development of oral chemotherapy is not straightforward. Some patient populations such as those who have undergone upper G.I. tract or head and neck surgery and children may not be good candidates for oral treatment. Factors such as food, age and concomitant medications may all influence systemic bioavialability. Dosing issues also differ for oral drugs where there is a strong argument for "flat dosing" irrespective of body surface area. Development of an oral drug may, therefore, be more complex than for i.v. cytotoxics and require more detailed pharmacokinetic studies and evaluation of potential interactions. These problems have, however, been overcome in other therapeutic areas and are now being addressed in oncology.

Funding of heath-care is an issue everywhere, although the specific concerns vary from country to country. Assuming equivalent efficacy, we can expect that patients would choose oral chemotherapy but will physicians be able and willing to follow their lead? A particular problem is that in some countries oral treatment may generate less income for the hospital and the doctor. Differences in reimbursement and physician remuneration between Europe and the United States mean that American oncologists may be less enthusiastic about oral chemotherapy. Oral treatment will reduce the number of in-patient and out-patient hospital visits with their associated medical and nursing, administrative costs; avoid the cost of disposables (e.g. infusion equipment, pumps) and decrease the pharmacy workload. Currently, chemotherapy costs account for about 5% of the direct cost of cancer care so it should be possible to set increased drug costs against the substantial savings that will be made elsewhere. Drug budgets are, however, easily identified and this process will be easier in some countries than in others.

Plenary Session

667

Cancer clinical trials - the key to improving outcome

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Improvements in outcome for cancer patients must be built on evidence and not on opinion (even expert opinion). Various agencies have established guidelines for treatment of common types and stages of cancer that are based on a hierarchy of clinical trials, with large randomised trials and meta-analyses providing highest levels of evidence. However, in assembling the evidence, it is important to evaluate (i) the quality of clinical trials, (ii) whether patients recruited to the trials were representative of those with similar type and stage of cancer, and (iii) whether there was bias in selection of trials.

A systematic method for evaluating the quality (or "internal validity") of a clinical trial is to ask the following:

1. Does the study address an important question?
2. Is the design of the study appropriate? (i.e. randomised design and blinding if feasible, sample size and statistical issues; explicit definition of primary endpoint)
3. Are the endpoints of the study appropriate – do they reflect benefit to patients (overall survival, quality of life) or merely biological activity (tumour response)?
4. Do the analysis and report of the study truly reflect its results?

Trials should also be examined for consistency with clinical experience and with the results of other relevant trials ("external validity"). Important trials should always be repeated before their results are used to change the standard of care.

Patients are often selected for inclusion in clinical trials (e.g. by high performance status) and it is important to ask whether the results of the trial can be generalised to other cancer patients.

We have shown that even large randomised cancer trials are subject to publication bias whereby those with negative results are delayed in publication in comparison to positive trials, or are not published at all. This can cause serious bias in compiling evidence; it is imperative to seek evidence of publication bias when compiling evidence.

Overall, improving outcome for cancer patients requires that the right treatment be given, that it be given well, and that it be given with compassion and support. Clinical trials provide the key to the first of these requirements, and treatment of patients within the context of a clinical trial may help to ensure the second, and contribute to the third. It is perhaps for these reasons that patients recruited to clinical trials may have better outcome as compared to similar patients who are not included in clinical trials.

668

The usefulness of meta-analysis in decision making

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In all the important decisions we make in life information and evidence is key. In medicine, the randomised controlled trial is universally acknowledged as providing key unbiased information which is the foundation for evidence-based medicine. High quality meta-analyses go a step further than the individual trial by trying to obtain as complete a picture as possible by summarising the results of *all* the relevant randomised trials. In this presentation we discuss how meta-analyses have reliably shown which treatments are effective, which are not and also identified some, which have been positively harmful. Without these meta-analyses we argue that we would still be unsure as to the value of a number of these treatments. Nevertheless, it is unrealistic to expect that an individual trial or meta-analysis will give "prescriptions" on how each individual patient should be treated, rather it gives guidance on how populations of patients with a certain disease should be treated. Thus, a useful way of considering the interpretation of a meta-analysis showing a positive result for a new treatment is that it should change the stance of the doctor (and patient), from one of "is there any good reason why I should use this new treatment in this patient?" to "is there a good reason why I should not use this new treatment?". Meta-analyses are also critical for helping us decide on the direction and focus for future research. At its simplest level a high quality meta-analysis summarises what has been done and what the outcomes were. If we do not have this information when designing a new trial, we argue that we are in danger of undertaking inappropriate and unethical research. Finally, we argue that unless we plan better for the future, meta-analyses will not be as informative as they have been in the past.