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Review

Achievements and future of chemotherapy

J. Verweij *, M.J.A. de Jonge

Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

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Abstract

Although surgery and radiotherapy result in a cure in 40% of all cancer patients, the remaining 60% of the patients die as a result of metastatic disease. For those patients cancer has to be considered as a systemic disease and cure from cancer will likely come from some type of systemic treatment. This article gives a brief overview of the achievements in the development of chemotherapy over the last 50 years and the new potential targets for further drug development.

Keywords: Chemotherapy; Review; Achievements

1. Introduction

While surgery for cancer was already reported centuries ago, practical limitations restricted its use. With the advent of anaesthesia its use became more widespread and for more than 100 years surgically removing tumours has now become a standard of care. After the discovery of the principles of radiotherapy this technique was rapidly developed and also became a standard treatment quite some time ago. In contrast to those two treatment modalities, chemotherapy is a relatively young strategy. The first steps in its development were made in the late 1930s, and followed-up at the end of the Second World War. Since the late 1950s, in particular, there has been steadily increasing interest in the development of drugs against cancer. The relevance of this development should not be underestimated. While surgery and radiotherapy beyond any doubt have their merits and result in a cure for some 40% of all cancer patients, the remaining 60% die as a result of metastatic disease. For those patients cancer has to be considered as a systemic disease and cure from cancer will likely come from some type of systemic treatment. Chemotherapy could be such a systemic therapy.

The term 'chemotherapy' is actually confusing since it suggests therapy with a chemical, and the vast majority of drugs could easily be considered as chemicals even though they might not be used in cancer therapy. 'Cytotoxic' therapy is a better description of what is meant. The treatment aims at killing the cancer cell through a direct effect. Cytotoxic therapy would also be easier to differentiate from the 'cytostatic' therapy that is currently in development and will be discussed later in this article. In the following text the historic term 'chemotherapy' will, therefore, relate to cytotoxic treatment.

In the 50 years of its development, chemotherapy has yielded important achievements. While the most important effect is an improvement in survival [1], it is obvious that in this respect gains have to be balanced against toxicity in indications where efficacy is limited. However, palliative effects such as symptom control and an increase in quality of life cannot be ignored. These can be achieved with chemotherapy as well. The present review is intended to highlight certain achievements without claiming to be a complete overview of this field.

2. Cure by chemotherapy

Certainly among non-oncologists there is limited awareness of the curative potentials of chemotherapy, which can occur frequently in spite of the extensive spread of disease. In several diseases, particularly a few that were extremely lethal before the era of chemotherapy, chemotherapy can now be considered the main curative treatment.

* Corresponding author. Tel.: +31-10-4391338; fax: +31-10-4391003.

E-mail address: verweij@onch.azr.nl (J. Verweij).

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The treatment of metastatic germ cell tumours with chemotherapy can be considered as one example of the success of modern medical oncology. The first advance in the treatment of germ cell tumours was achieved in 1960 with the introduction of chlorambucil, dactinomycin and methotrexate resulting in tumour regression in 30% of patients [2]. The next major improvement came with the recognition of the efficacy of cisplatin [2]. Currently, approximately 70–80% of patients presenting with metastatic disease can be cured with cisplatin-based chemotherapy [3]. Given the fact that this diagnosis is typically made in early adulthood, this success must be judged not only in terms of the high cure rate, but also by issues of survival and, in particular, minimisation of the risks of late treatment toxicity since significant adverse events continued to be observed including myelosuppression, Raynaud's phenomenon, pulmonary toxicity, neurotoxicity and nephrotoxicity. Factors associated with treatment failure have also been analysed and enable a more differential treatment approach. Based on several independent prognostic factors, patients with metastatic germ cell tumours can be allocated to three prognostic categories: good prognosis (5-year survival = 90%), intermediate prognosis (5-year survival = 75–80%) and poor prognosis (5-year survival = 48%) [4]. Using these prognostic factors, the main goal of trials in patients with good-risk disease, is to reduce the toxicity of the standard four cycles BEP (bleomycin, etoposide, cisplatin) chemotherapy, while retaining the efficacy. In intermediate and poor-risk patients, trials are focused on high-dose regimens and the incorporation of new drugs to improve the prognosis.

Chemotherapy also had a major impact on the cure rate of female patients with choriocarcinoma. Before the introduction of methotrexate, choriocarcinoma resulted in the death of 60% of patients with disease confined to the uterus and 90% of those with metastatic disease [5]. As for testicular cancer, the treatment of these patients is currently also based upon prognostic factors. Good-prognosis patients are treated with single-agent methotrexate resulting in a 100% cure rate. In intermediate and high-risk patients combination chemotherapy is the treatment of choice.

In the management of Hodgkin's and non-Hodgkin's disease, the development of chemotherapy resulted in a major improvement in survival. From the time of discovery by Roentgen until the middle of the 20th century, Hodgkin's disease was treated by radiation only [6]. In the 1940s, nitrogen mustard was discovered to have important lymphocytolytic effects in patients with malignant lymphomas. This actually constituted the beginning of the era of chemotherapy. By 1964, experimental studies indicating the desirability of using combinations of cytotoxic agents with non-overlapping toxicity profiles led to the introduction of the combination of mechlorethamine, vincristine, procarbazine and prednisone (MOPP) resulting in major responses in 81% of patients with advanced disease with an overall cure of 48% [7–11]. Many modifications of this regimen have subsequently been studied. However, none of them proved to be superior in any sense. The first entirely new regimen developed was ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) [12,13], which was designed in 1975 to specifically treat MOPP-resistant disease.

Until recently, radiotherapy has been the traditional treatment for early stage Hodgkin's disease. However, the emerging awareness of early and late complications of mantle or total lymphoid radiotherapy consisting of pneumonitis, constrictive pericarditis, occlusive coronary artery disease, cardiomyopathy [14,15] and an increased risk of secondary malignancies, and the fact that similar response and cure rates can be achieved by systemic chemotherapy but without the comparable morbidity, will probably result in the implementation of chemotherapy as the treatment of choice also for patients with early stage disease.

The non-Hodgkin's lymphoma constitute a heterogeneous collection of neoplasms with many different clinical manifestations and histologies. A major breakthrough in the treatment of advanced aggressive lymphoma was the introduction of CHOP chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone. The more complicated regimens combining six or more cytotoxic drugs, which were studied over the last years, did not improve the outcome in unselected patients with aggressive lymphoma [16], indicating that CHOP induction therapy is still the standard of care, yielding a cure rate of 40% in unselected patients. However, this figure also means that further, even more effective, treatment strategies need to be developed.

Even more marked than in the treatment of solid tumours, the care of the patient with leukaemia, particularly acute leukaemia, depends on the ability to support the individual through the complications of therapy. Infection and haemorrhages are the primary causes of death in leukaemia patients [17], and most of the improvements seen in the care of leukaemia patients over the last decades can be directly attributed to advances in supportive care, thereby facilitating chemotherapy. Standard-dose induction chemotherapy regimens for adult acute myeloid leukaemia (AML) based on the combination of cytarabine with daunorubicin yields complete responses ranging from 50 to 75% [18]. New intensified post-remission therapies have significantly improved the outcome in patients with AML. However, the optimal role of intensified treatment and marrow transplantation has yet to be determined [19].

For patients with acute lymphoblastic leukaemia (ALL), current induction and consolidation treatment

with intensive multi-agent chemotherapy combined with central nervous system prophylaxis results in complete remission in 80–90% of cases with long-term survival in 30–40% [20]. Although maintenance therapy is a standard component in the treatment of paediatric ALL, optimal maintenance therapy in adults remains controversial.

3. Adjuvant chemotherapy

As indicated, for many solid tumours, a certain level of incurability is still a reality. The incurability mostly relates to residual cancer in an occult and microscopical stage, eventually leading to the outgrowth of metastases. At this stage, local therapy apparently fails to be sufficient and systemic therapy may be attractive. It is actually at this stage where over the years some important achievements have been made. The following are examples.

One of the diseases where adjuvant (postsurgery) chemotherapy has had a major impact is breast cancer. A meta-analysis of direct patient data, involving 69 trials and 29 769 patients, was published in 1998 [21]. Of these, 47 trials including 17 723 patients compared adjuvant chemotherapy with no chemotherapy. Chemotherapy led to a significant reduction in recurrence as well as an increase in survival in patients under the age of 70 years. For those older than this, insufficient data were available to draw conclusions. The proportional reductions in risk were similar for women with node-negative and node-positive disease, and independent of menopausal status. While adjuvant chemotherapy had already been accepted as a standard for premenopausal patients with node-positive disease based on independent trials, the outcome of the meta-analysis has considerably changed practices for all other patients as well.

In view of reported response rates to chemotherapy, breast cancer, even when metastatic, has always been considered as a relatively chemosensitive disease. As such, the outcome of adjuvant chemotherapy, which is given for microscopic residues, may not be surprising. In contrast, colon cancer has always been considered as relatively chemotherapy-resistant once it has metastasised, with much lower response rates being reported. Nevertheless, as early as 1988 [22], a meta-analysis suggested a potential benefit of adjuvant 5-fluorouracil (5-FU)-based chemotherapy. Boosted by the positive results of the North Central Cancer Treatment Group (NCCTG) study [23] comparing (in metastatic patients) the combination of 5-FU and levamisol with no chemotherapy, many other trials were started. Currently, there seems to be a consensus that six cycles of 5-FU with leucovorin can be considered as standard adjuvant therapy for Dukes' C colon cancer [24,25]. Improvements in the 5-year survival from 63–77% without chemotherapy to 75–84% with chemotherapy appear achievable [26], thus improving the survival of hundreds of thousands of patients worldwide. As yet, a similar conclusion cannot be drawn for Dukes' B2 colon cancer patients [27].

An exceptionally large benefit from adjuvant chemotherapy was found in children with osteosarcomas [28]. In a small sample size of only 36 patients randomised to either adjuvant chemotherapy or no chemotherapy, the difference in relapse-free survival was so large (17% for the control group versus 66% for the treated group) that it was evident that extending the sample size would not lead to another conclusion. Moreover, the results were comparable in 77 additional patients who declined to undergo randomisation but elected observation or chemotherapy.

4. Concomitant chemoradiation therapy

Given the efficacy of radiation, the notion of cancer being a systemic disease for many patients, and the improved results of chemotherapy, the latter has also been combined with radiotherapy in the treatment of locally advanced cervical cancer and squamous cell cancer of the head and neck region (HNSCC) with nodal involvement in an attempt to reduce the rate of local failure and distant metastases and thereby improve overall survival and organ preservation.

Despite screening programmes, locally advanced cervical cancer is present in approximately half of the patients at the time of diagnosis. Until now pelvic irradiation with external beam- and brachytherapy has been the standard treatment for locally advanced cervical cancers (stages IB2-IVA) [29]. The ability of radiotherapy to cure locally advanced disease is limited by the size of the tumour, because the doses required to treat large tumours exceed the limit of toxicity in normal tissue. For stage IIB, 5-year survival ranges from 63 to 70% and for stage IVA from 16 to 25%. The main cause of death among women with cervical cancer is uncontrolled pelvic disease. The primary goal of concomitant chemoradiotherapy has largely been to use cytotoxic agents to sensitise tumour cells to the effects of radiotherapy. Concurrent chemotherapy inhibits the repair of sublethal damage from irradiation, synchronises cells to a particularly radiosensitive phase of the cell cycle, reduces the fraction of hypoxic cells that are resistant to radiation and initiates proliferation in non-proliferating cells. Chemotherapy may also independently increase the rate of death of tumour cells. Four recent large randomised trials have studied the impact of concomitant chemoradiotherapy on the survival of patients with locally advanced cervical cancer [29–32]. In all four trials, administration of cisplatin concomitant

to radiation therapy improved survival in patients with bulky stage IB disease and in patients with stage IIA–IVA disease. Since only 30% of the patients studied had stage III or IVA disease without involvement of lymph nodes outside the pelvis, confirmatory data are required [33,34]. Currently available data do not allow definitive conclusions to be drawn as to which drugs or regimens are optimal in the treatment of cervical cancer. It seems reasonable, however, to suggest that cisplatin-based chemotherapy should be given.

The integration of chemotherapy in the therapy of patients with locally advanced HNSCC has also been pursued with the goal of increasing survival rates and organ preservation. Induction (neoadjuvant) chemotherapy consisting of a combination of cisplatin and 5-FU resulted in a significant tumour regression in 60–90% of the patients with a complete response in 31–66% and a reduction in the occurrence of distant metastases [35–37]. Neoadjuvant chemotherapy, however, had no impact on the loco-regional control of the disease and did not improve survival compared with either surgery or radiotherapy alone. Therefore, the routine use of up-front chemotherapy cannot be recommended as standard treatment. Induction chemotherapy in combination with radiotherapy did, however, enable the preservation of the ability to speak and swallow without compromising the cure rate in patients with operable stage III and IV laryngeal and hypopharyngeal cancers, thereby improving the quality of life of these patients [38].

In patients with locoregionally advanced inoperable disease there are now multiple positive randomised trials and positive meta-analyses providing evidence that radiochemotherapy improves survival and locoregional control compared with radiotherapy alone in patients with cancer of the oropharynx [39–45]. However, the addition of platinum and 5-FU-based chemotherapy to radiotherapy substantially increased mucocutaneous toxicity resulting in weight loss and a requirement for tube-feeding. Treatment interruptions were longer for patients in the combined modality group, but there was no difference in the overall treatment time or the frequency of treatment interruptions. Although chemoradiation therapy results in preservation of the organ, this does not equate to preservation of the organ function. Severe and chronic mucosal injury and tissue fibrosis as a late toxic effect of intensive radiochemotherapy regimens may leave patients with poor speech and swallowing function. Non-surgical and surgical approaches to organ-function conservation need to be evaluated, with attention to objective assessments of speech and swallowing function, in addition to local control and survival [42].

Despite the reported limitations, these data also provide a basis to study the chemoradiation approach in other diseases that are responsive to both modalities.

5. Quality of life

Although the goal of treating patients with cancer is to cure, this is not possible in many cases and the objectives become prolongation of life and the maintenance of its quality. However, 'quality of life' is a concept difficult to define. Both the disease and its treatment have many effects on the patients resulting in disease-related symptoms and treatment-related symptoms. Unfortunately, measurement of quality of life (QoL) has been hampered by methodological problems: the lack of validated instruments, the often incomplete data collection and the difficulty in determining the clinical relevance of statistically significant changes in QoL scores.

Until recently, the role of chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC) was controversial. The meta-analysis demonstrated a modest impact of cisplatin-based combination chemotherapy on survival compared with supportive care, resulting in an improvement in the median survival of 1.5 months [46]. However, toxicity induced by chemotherapy might outweigh the benefit of a modest extension of life and the temporary relief of disease-related symptoms. A recent randomised study demonstrated that treatment with cisplatin-based combination chemotherapy of patients with metastatic NSCLC resulted in an improvement of QoL, implying that palliation by chemotherapy outweighed short-term toxicity [47]. Other studies in patients with metastatic NSCLC have also reported symptom improvement resulting from chemotherapy treatment [48–50].

The impact of chemotherapy on quality of life and survival was also assessed in patients with metastatic colorectal cancer who had failed on 5-FU. Two randomised trials compared second-line treatment with irinotecan either with best supportive care or high-dose 5-FU infusion [51–53]. In both trials, median survival was improved by 2.3–2.7 months in patients randomised to treatment with irinotecan. In the comparison against best supportive care, treatment with irinotecan resulted in a significantly better quality of life, except for diarrhoea. These results indicate that despite the side-effects of treatment, second-line chemotherapy with irinotecan results in fewer tumour-related symptoms and a better quality of life compared with supportive care alone in patients with advanced colorectal cancer. Assessment of the impact of chemotherapy on the quality of life of patients will become more and more important, especially in subsets of patients in whom cure is not achievable.

6. New cytotoxic drugs, a focus on different targets

Over the decades the search for new agents against cancer has become increasingly systematic and increas-

ingly focused. In the 1980s special attention was given to the development of analogues with the hope of developing agents that were either more efficacious or at least as efficacious as the parent drug, but with less toxicity. The search for analogues has unfortunately not been very rewarding and only a few agents have been added to the chemotherapeutic armamentarium. In the 1990s, there has again been a shift towards the development of new classes of agents although the term 'new' might not always be fully appropriate. The two most successful classes developed in the last decade have been the taxanes and the topoisomerase I inhibitors. Interestingly, the model compounds of both of these classes (paclitaxel and camptothecin) were both discovered in the 1960s by the same group of investigators headed by Dr Munroe Wall. Both underwent a similar developmental history with initial rejection based upon formulation issues and toxicity, respectively, with a clear revival in their development in the late 1980s and the early 1990s.

Taxanes promote the polymerisation of tubulin into stable microtubules and inhibit microtubule depolymerisation. This leads to a disruption in the equilibrium within the microtubule system and ultimately leads to cell death [54–57]. They appeared extremely active in model systems and interestingly initial clinical activity was already noted in the early phase I clinical studies. While the development of paclitaxel was delayed considerably by the occurrence of hypersensitivity reactions, the development of docetaxel has been one of the most rapid in the history of anticancer drug development. Both agents have meanwhile been registered and have found their place in our standard treatment approaches.

Paclitaxel was first registered for second-line use in ovarian cancer, but is currently considered standard first-line chemotherapy for ovarian cancer, in combination with cisplatin. After it was shown that paclitaxel and cisplatin could be combined at high doses [57] the first randomised study comparing cisplatin + paclitaxel with cisplatin + cyclophosphamide indicated a considerable survival benefit for patients with ovarian cancer [58]. Subsequently, a study of similar design applying paclitaxel as a 3-h infusion instead of a 24-h infusion yielded similar results with a benefit for the paclitaxel combination [59]. Based upon these studies, this combination has become standard practice, although there are still some issues that need further clarification [60,61]. Whether carboplatin can replace cisplatin in this combination is a matter of ongoing debate and will require the reporting of long-term survival of recently completed studies. In general, the combination of cisplatin + paclitaxel seems to yield a survival benefit of approximately 5 months and a response rate increase of approximately 13%.

More recently, paclitaxel has also been registered for the treatment of patients with metastatic breast cancer failing anthracyclines, as well as for first-line chemotherapy in NSCLC, the latter again in combination with cisplatin.

For docetaxel, the initial development has largely focused on the treatment of breast cancer where the agent is also registered for second-line treatment after anthracycline failure. An interesting feature of docetaxel is the fact that the drug is unusually active in the treatment of liver metastases from breast cancer, a stage of disease that is commonly less sensitive to chemotherapeutic intervention. Response rates as high as 40–60% with docetaxel in patients with liver metastases have been reported.

The nuclear enzyme topoisomerase I plays a crucial role in the normal replication of DNA. In its physiological state in the chromosome, the DNA helix is supercoiled. Replication requires transient relaxation and unwinding of the parent DNA. In order to achieve this, transient cleavage of the DNA is required mediated by the formation of a cleavable complex consisting of a covalent intermediate between topoisomerase I and DNA, allowing passage of the intact strand. The enzyme-bridged breaks are resealed afterwards. Topoisomerase I inhibitors stabilise the cleavable complex, thereby inhibiting the religation step [62–64]. This results in collision of the replication fork and, finally, in double-strand breaks and cell death [65]. Although the activity of the parent compound camptothecin was already noted in the early 1970s, the fact that it exerted its activity through the inhibition of topoisomerase I was only identified in the late 1980s. The latter has stimulated further research into specific inhibitors of the enzyme topoisomerase I, aiming for agents with less toxicity than that obtained with the parent compound camptothecin. Meanwhile two of these, irinotecan and topotecan, have been registered for use in metastatic colorectal cancer and second-line treatment of ovarian cancer, respectively.

Irinotecan is currently considered the standard of care in the second-line treatment of metastatic colorectal cancer failing 5-FU treatment. In a randomised trial [51], the survival of the treated group was significantly ($P = 0.0001$) better than that of patients on supportive care only, with the already discussed benefits in QoL [51]. Moreover, in a direct comparison with a change in the means of 5-FU administration [52] irinotecan turned out to be significantly superior. More recent studies [66,67] suggest that the combination of irinotecan with 5-FU in the first-line treatment of metastatic colorectal cancer is superior to single-agent 5-FU, in terms of response, time to progression and overall survival. Clearly the introduction of irinotecan has marked a total change in the until now grim prognosis of metastatic colorectal cancer.

Topotecan has been registered for use as second-line treatment in patients with advanced ovarian cancer. In a

randomised trial the efficacy of topotecan was compared with paclitaxel in patients who had progressed during or after one platinum-based chemotherapy regimen [68]. Treatment with topotecan resulted in a response rate of 20.5% compared with 13.2% for paclitaxel. The median time to progression after therapy with topotecan was significantly longer (9 weeks, $P=0.002$). As paclitaxel is moving to first-line therapy, topotecan represents an important new treatment option for patients with ovarian cancer that progresses after first-line therapy.

7. Dosing

One of the interesting aspects of chemotherapy is that it is dosed based on body surface area (BSA). This is usually based upon a belief that this way of dose calculation yields a more precise and individual dosing. This, in turn, is considered important because of the relatively narrow therapeutic window of these agents. However, the basic assumptions behind this dosing are not based on scientific evidence of superiority [69], which seems to be unknown to the majority of medical oncologists. BSA as a basis for dosing was introduced to enable the projection of mice lethal dose (LD) 10 doses to starting doses of phase I clinical trials [70], and not as a measure for further dose individualisation! BSA is not measured but estimated based on a formula developed in 1916. Evidence that this way of dosing is indeed better that simply using a flat dose is lacking, perhaps with the exception of its use for docetaxel and gemcitabine. On the contrary, available data suggest dosing based on BSA is as inaccurate as simple flat dosing [71–73], whilst it increases the risk of mistakes in calculations. BSA fails to standardise the marked interpatient variations in pharmacokinetics [74]. With all the achievements of chemotherapy, the time has come to reconsider dosing mechanisms, and wherever appropriate to develop more reliable and scientifically supported means of individualised dosing [72]. The dosing of carboplatin [75] based on formulae developed from pharmacological observations is a good example of a better approach.

8. Molecular targeting, cytostatic agents

Recent achievements in the field of molecular biology have further unravelled many of the processes in the development and growth of cancer cells, as well as factors in the microenvironment that are a prerequisite to this growth and to the metastatic potential of cancer cells. The Human Genome Project has resulted in a true plethora of potential targets for anticancer drugs. Actually, since the number of potential targets has now become endless it is likely that the art of drug development will become choosing the right target, rather than anything else. It is impossible to list all of those new targets and we will limit our narrative to mentioning just a few, since agents involving these targets are already in clinical trial.

It has long been recognised that the new formation of blood vessels (angiogenesis) is an absolute necessity for tumours to grow and survive. Thus, this process seems to be an attractive target [76]. Leading targets in this sense that have been identified thus far are the inhibition of matrix metalloproteinases (MMPs), the antagonism of the vascular endothelial growth factor (VEGF) pathway of angiogenic induction, and the inhibition of $\alpha_v\beta_3$-integrin-vitronectin interaction that is pivotal in mediating endothelial cell adhesion to the extracellular matrix during the above mentioned neovascularisation.

Extracellular proteases are essential for tumour cells to be able to penetrate the basement membrane. Proteolytic degradation of the extracellular matrix (ECM) is also necessary when invasive tumour cells penetrate tissues, gain access to blood vessels, exit blood vessels and colonise distant sites (metastases). In addition, angiogenesis involves active proteolytic degradation of the ECM by invasive endothelial cells [77]. MMPs can be classified into four groups: collagenases, gelatinases, stromelysins and membrane-type metalloproteinases [77]. In cancer, there appears to be a local and temporal imbalance between the levels of activated enzymes and their inhibitors. This imbalance results in a breakdown of the extracellular matrix. MMP inhibitors (MMPIs) were first considered as potential antimetastatic agents. MMPI treatment may also directly suppress the growth and development of lymphatic metastasis, whilst the anti-angiogenic properties of these drugs may relate to the inhibition of haematogenous metastases [78]. Numerous inhibitors of these inhibitors are currently in clinical development. The most advanced development is with the matrix metalloproteinase inhibitor Marimastat that in a recently completed randomised trial has shown an efficacy similar to that of gemcitabine in metastatic pancreatic cancer, but with a potentially improved therapeutic index.

A large number of cellular oncogenes and tumour suppressor genes continue to be identified. These oncogenes and tumour suppressor genes encode proteins which are involved in the pathways through which cells sense their environment and respond to it (cell signalling), particularly with respect to controlling cell proliferation, differentiation and death [79–83]. These proteins function at each of the crucial steps in the transfer of information from growth factors binding to the cell membrane, through to the read-out of specific genes in the nucleus. In many instances the proteins involved in normal signalling are overexpressed in cancer. Hence, a downregulation of over-

stimulated transduction pathways might lead to the inhibition of tumour growth more than would be the case in normal tissues [84–87]. Ideally, removal of proliferation-promoting signals from cancer cells would force the tumour cell into a quiescent state, leading to an overall inhibition of tumour growth. Thus, we may expect that drugs that act by inhibiting cell signal transduction pathways will have a cytostatic rather than a cytotoxic (cell-kill) effect. As an example, considerable effort is focused on the development of receptor tyrosine kinase inhibitors and ras, which are on the 'linear' pathway from receptors to transcription factors.

Telomeres constitute yet another new target for antitumour therapy. Telomeres are ends of eukaryotic chromosomes that protect free DNA ends from end to end fusions and exonucleosytic degradation [88]. During cellular replication both strands of DNA separate and daughter-strands are synthesised in a slightly different manner on the leading and lagging strands, whilst the lead strand replicates in a continuous fashion, the lagging strand replicates in a discontinuous fashion. This results in 'end replication imbalance', [89,90] that can lead to a loss of 50–200 base pairs with every cell division [91], with the eventual shortening of the telomeres to a length that coincides with the activation of an antiproliferative mechanism termed mortality stage 1 (M1). At this stage, senescence in somatic cells occurs because of the induction of *p53* and other genes [92]. Thus, telomere shortening functions as a 'mitotic clock' [93], limiting division in somatic cells to 50–70 times [94], thereby contributing to cellular ageing. In some cells, the M1 stage is bypassed until telomeres become critically shortened (mortality stage 2, or M2). At this M2 stage, a specialised DNA polymerase called telomerase appears and neutralises its internal RNA template to synthesise the telomeric sequence and compensate for the loss of telomeric DNA due to the incomplete replication. This prevents further shortening of telomeres and stabilisation of their length and contributes to immortalisation. Telomerase activity is high in various tumours, but repressed in most normal human tissues [95,96], a difference that can be used as a potential target of antineoplastic treatment.

As already indicated, preclinical studies showed that inhibitors of all of these new targets can be described as cytostatic drugs. Thus, the aim of their long-term use would be to create a state of tumour 'dormancy' by halting proliferation, and thus generating disease stabilisation. The expected long-term treatment requires minimal side-effects and an easy administration schedule in order not to limit drug compliance. The recommended therapeutic dose will thus not be based on the maximally tolerated dose, but on a dose with optimal biological effect. The fact that these drugs are thought to generate disease stabilisation only might also influence the further development strategies, and will have major consequences for trials design. Phase II studies, in which the response rate is determined for treatment with a new agent, might become superfluous.

As one may have noted, many of the 'breakthrough' trials that are referenced above, have been performed by cooperative groups. Hopefully, the recent marked increase in budget for the National Cancer Institute in the USA, will also increase the number of important pivotal trials performed by NCI-related cooperative groups. In this respect, it is disappointing that in Europe a similar political support for cancer research is largely lacking and actually it is amazing how European investigators nevertheless succeed in playing a key role in treatment development and refinement.

9. Conclusion

Over the last few decades chemotherapy has evolved to become an important integral part of the multidisciplinary approach to the treatment of cancer. In a limited number of cases chemotherapy has become the backbone of curative treatment. In a larger number of cancers relevant survival benefits, as well as relevant improvements in quality of life, can be achieved.

Recent molecular biological research has yielded an extremely high number of new potential targets for drugs against cancer. Selecting the most appropriate of these targets will be very important. A shift towards inducing tumour dormancy rather than tumour cell-kill may be related to the development of these new agents, and this will have major implications for trial design.

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