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Perspectives in cancer chemotherapy

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When, in 1971, President Nixon signed the National Cancer Act in the USA, there was much optimism about the possibility of 'conquering cancer' and ending the burden of suffering and death caused by the numerous diseases grouped under the single heading of cancer.

Now, at the beginning of 2000, substantial progress has been made, but relatively little has been achieved in terms of reducing cancer mortality. The mood now, therefore, is one of more rational scepticism about major advances in the short or medium term.

Numerous efforts are being made around the world, and precious new knowledge has been gained, leading to new preventive and therapeutic approaches. So far, however, this has failed to change the natural history of most cancers, although cancer treatment now accounts for 6–15% of the total health expenditure in developed countries [1].

There are some exceptions, with promising success rates, mostly due to prevention and screening campaigns which may teach scientists and clinicians which paths to follow for the majority of therapy-resistant tumours. Successes in children, adolescents and young adults have been encouraging over the last two decades [2].

This article will attempt to review the achievements, covering the therapeutic results, in general, and the role of chemotherapy, in particular.

Data on cancer incidence and mortality help understand and quantify how successful therapeutic interventions have been. Clinical results with a few new chemotherapeutic agents in selected tumours (colorectal and lung) will be summarised. At this point, it is interesting to see which anticancer drugs have been approved by the European Medicine Evaluation Agency (EMEA), the European body whose task it is to make new drugs commercially available in 15 European countries.

Finally, some of the most promising ways of chemoprevention and the new drugs or therapeutic strategies now being or shortly to be developed will be considered, and the major obstacles such as mechanisms of resistance which, together with other factors, are believed to be responsible for therapeutic failure will also be examined.

1. A critical evaluation of past and present cancer chemotherapy

1.1. Epidemiology of cancer therapy

To put the results of cancer therapy into perspective, it may be worth recalling what has been achieved for other common diseases. For instance, the advent of antibiotics has enormously reduced in industrialised countries the mortality caused by infections; effective antagonists of histamine-2 receptors have led to a comparable reduction of mortality from gastric ulcers [3]; the development of fibrinolytics [4], platelet anti-aggregating agents [5], and n-3 unsaturated fatty acids have cut at least one-third off the mortality from myocardial infarction [6], the polio vaccine is responsible for the disappearance of poliomyelitis [7], and the hepatitis B virus (HBV) vaccination has led to a substantial decline not only of hepatitis, but also of liver cancer.

No such estimates can be made for cancer; this is because cancers are in reality an array of different diseases. Furthermore, it is hard to establish the role of therapy (surgery, radiation or chemotherapy, alone or combined) when at the same time improvements in diagnostic procedures have made earlier diagnosis possible, with consequent increases in survival [8]. Decreases in mortality from cancer are consequently not necessarily all the result of better treatment, although progresses in surgery since the 1950s have contributed substantially to the progresses in the survival rates registered for several (common) cancer sites [9,10]).

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Cancer incidence and mortality have risen steadily throughout the last century in most parts of the world. However, in the last few decades, there has been a modest, but encouraging, decline in cancer mortality in North America and Western Europe [1]. Thus, between 1990 and 1995, age-standardised cancer mortality rates for all neoplasms in the USA declined by 3.1% for both sexes combined [11]. About half of this decline was attributed to the levelling out of the epidemic of lung and other tobacco-related cancers, and the remainder to several factors, including reduced exposure to occupational carcinogens, prevention and early diagnosis, and improved treatment.

Within the European Union (EU), mortality from all causes declined by 43% between 1960 and 1994, but total cancer mortality rates in both sexes combined increased by 4.4%, reaching a peak in 1988 [12]. However, they had declined by 7% in 1994. Likewise, lung cancer rates in both sexes combined increased by 59% between 1960 and 1988, but declined by 14% between 1988 and 1994. Thus, over one-third of the decline in the last few years was accounted for by lung cancer alone, and approximately half by all tobacco-related tumours. Approximately half of the decline in total cancer mortality not attributable to tobacco included a steady fall in mortality from gastric cancer, for reasons that are however, still poorly understood (Table 1).

Fig. 1 gives the trends in mortality from major cancers in males and females in the EU over the period 1955–1994. Oral and pharyngeal and oesophageal cancer rates rose up to the late 1980s, mostly in males, but levelled off over the last few years. For women, there was a steady rise in lung cancer mortality (from 8.9 to 9.6 per 100 000), although female lung cancer rates were, and still are, relatively low in the whole EU compared with the United States [13,14]. However, favourable trends were observed for the first time for female breast cancer mortality in the UK [15] and in the EU as a whole, as well as for large bowel cancer [16]. Death rates were approximately stable for ovarian cancer, and the long-term declines in mortality from cancers of the stomach and of the cervix uteri continued. A modest rise was observed in pancreatic cancer rates, while leukaemia mortality had been steadily declining since the early 1970s.

Apart from the tobacco-related lung cancer epidemic in women, these figures therefore provide further evidence of a moderately favourable pattern in recent trends in mortality from major cancers in the EU, but it is difficult to understand and evaluate the underlying components, which include changes in risk factor exposure, including reduction of smoking in countries like the UK and Finland as well as the USA, which has resulted in a reduction in lung cancer in young and middle age males, screening, improved diagnosis and treatment. In the USA, the situation is not very different, despite the $27 billion spent on research since 1971. Fig. 2 compares the patterns of incidence and mortality in US for the various cancers in the period 1971–1991. Only testis, thyroid and bladder show considerable decreases in mortality, despite an increase in incidence. For some other cancers, i.e. Hodgkin's disease, uterus, stomach and uterine cervix, the drop in mortality is accompanied by a drop in incidence. For other cancers, mortality has either increased or changed only marginally [17]. Only recently has some moderate decline in cancer mortality been noted in North America [11].

2. Impact of screening and early diagnosis

Screening and early diagnosis have played their part in these favourable trends [18] and, although the role of screening goes beyond the scope of this paper, the main quantitative aspects will be mentioned here.

A more rational approach to cervical screening (Papanicolaou (Pap) test)) could further reduce the risk of this tumour, and avoid up to 1% of the total cancer mortality in some parts of Western Europe and an even larger proportion in Eastern Europe, South America and developing areas of the world.

It is also likely that wider use of mammography could reduce breast cancer mortality by 20–30% in women

Table 1
Age- and sex-standardised mortality rates per 100 000 (world standard population) from selected causes in the European Union, 1960–1994

	All causes	All cancers	Lung cancer	Stomach cancer	Other cancers	CPM[a]
Year						
1960	824.2	140.3	19.5	24.9	96.1	17.7
1970	737.5	145.0	25.2	19.3	100.5	19.7
1980	635.2	146.1	29.7	13.7	102.7	21.9
1988	541.9	146.7	30.9	10.6	105.2	24.7
1990	526.2	143.9	30.2	9.9	103.8	24.7
1992	507.6	142.6	29.7	8.7	104.2	25.2
1994[b]	468.0	133.1	26.9	8.2	98.0	25.8
Change in rate, 1988–1994	−73.9 (−13.6%)	−13.6 (−9.2%)	−4.0 (−12.9%)	−2.4 (−22.6%)	−7.2 (−6.8%)	

[a] CPM, cancer proportional mortality.
[b] Data were available up to 1992 for Belgium and 1993 for Denmark. Source: Levi and colleagues, modified [12].

aged 50–70 years, and perhaps lower mortality among those aged 45–50 years too. Early diagnosis and surveillance has proved useful for skin melanoma [19] and screening procedures have been proposed to reduce mortality from colorectal and prostate cancer. However, at present, we do not have enough data to provide quantitative estimates of the potential impact on these tumours and, consequently, to formulate indications on a public health level [18,20].

Screening and early diagnosis have also influenced other common neoplasms, including lung, stomach and ovary, and various approaches are being investigated [18]. Finally, screening and early diagnosis may influence cancer survival figures in various countries, and have to be borne in mind as a potential modifying factor for any inference on trends in survival [8,21,22].

3. Impact of newer therapies on cancer deaths

Any estimate of how progress in treatment may reduce mortality from cancer in Europe is subject to major uncertainty. Still, some 'reasonable' estimates of the proportions and numbers of avoidable deaths over the next decade in Europe are possible, at least for a few selected tumours [23,24].

For most common cancer sites, it is difficult to quantify the potential impact of improved treatment on survival [25–27]. For several of these tumours, there is little basis for suggesting any real improvement, but even for breast cancer, whose overall survival may have improved by 10%, this can easily be missed because of changes in incidence. Mortality, in fact, reflects changes in survival and incidence rates, but the latter are not available for long periods and not reliable enough for large areas and meaningful periods of time. Survival is also subject to major uncertainties depending on advances in the diagnosis of various tumours. Likewise, trends in incidence are greatly influenced by changes in diagnostic procedures.

Still, declines in mortality from breast cancer—independently from trends in incidence—have been registered in the UK [15], and in the EU as a whole [16].

There are, moreover, a few selected neoplasms or groups of neoplasms for which substantial progress in therapy has been achieved over the last few decades, and for which the corresponding impact of treatment on mortality rates is quantifiable. These are essentially

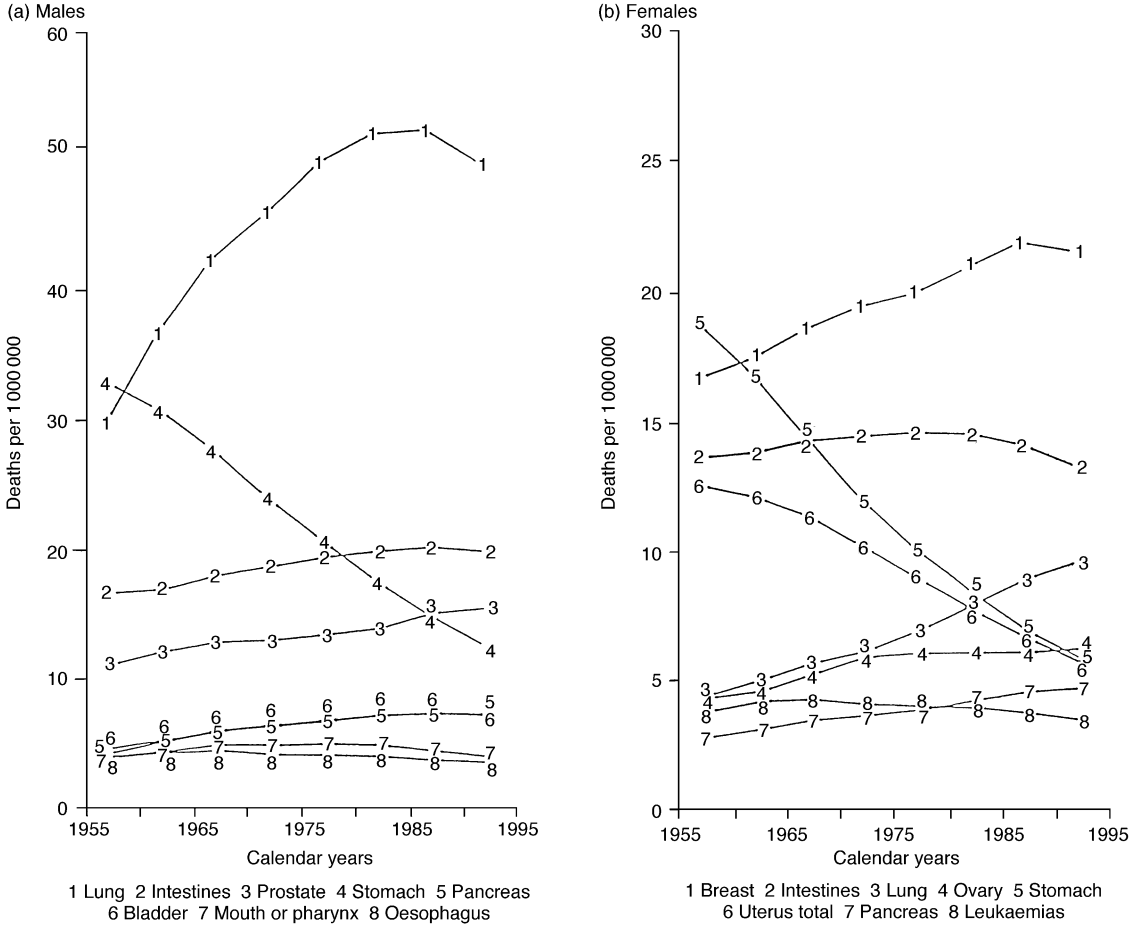

Fig. 1. Trends in age-standardised mortality rates (per 100 000), world standard) from major cancer sites in the 15 countries of the European Union, from 1955–1994. (a) males; (b) females.

lymphoreticular and germ cell tumours. For these cancers too, however, the availability and utilisation of effective therapies have not been uniform and timely in various parts of the world—nor within Europe—and the consequent impact in terms of deaths avoided has not been completely exploited.

Cancer control in developing countries can hardly be based on curative treatment given its costs and the fact that cancers which predominate in the developing world, stomach, lung and liver, are poorly responsive to treatment [28]. Interventions on smoking and HBV vaccination, in contrast, represent the most effective preventive strategies [29–32].

4. Hodgkin's disease

In Western European countries, mortality from Hodgkin's disease has fallen substantially, generally starting from the late 1960s or early 1970s [33,34]. The overall decline is over 60% for both sexes. This confirms that effective treatments have been adopted in Western Europe, although not uniformly. Consequently, there is still room for further improvements in several areas, not only in terms of further advances in the treatment of the disease but also as regards better implementation of available therapies [35].

In absolute terms, the declines in mortality from Hodgkin's disease in Western Europe correspond to the avoidance of over 4000 deaths per year, and this figure could well approach 5000 if the most favourable trends held true in all areas. The decline in mortality from Hodgkin's disease is much more recent and less consistent in most Eastern European countries [16]. If patterns comparable with those in Western Europe were observed in the East, a further 1000 deaths from Hodgkin's disease per year could be avoided.

5. Leukaemias

Leukaemias account for over 3% of the total cancer mortality in Europe and North America, and include a

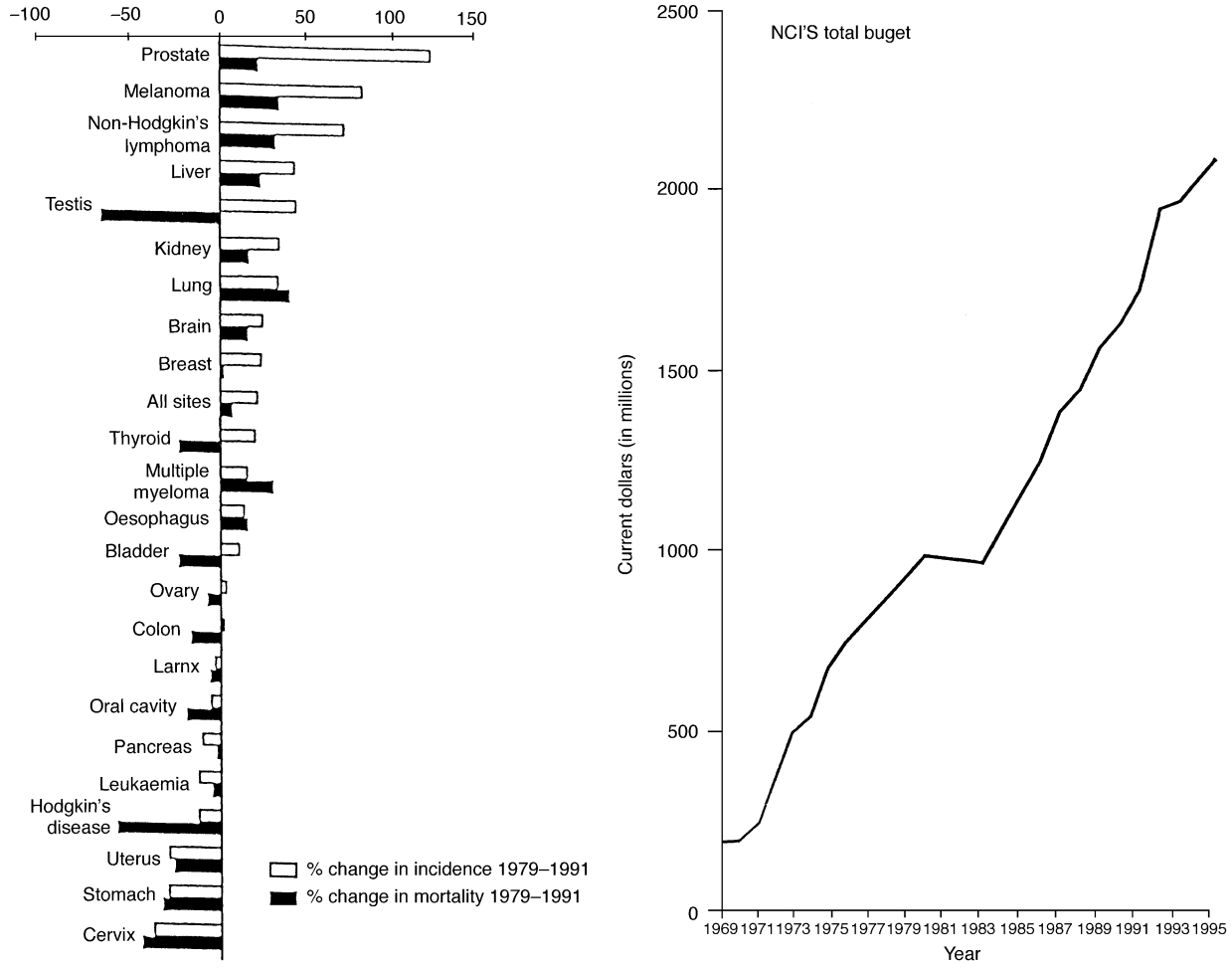

Fig. 2. Change in incidence and mortality of various cancers in US (on the left) and expenses for cancer research by the National Cancer Institute (on the right) [13].

number of different diseases whose response to treatment varies substantially. Efficacious chemotherapy for acute lymphoblastic leukaemias has been available since the late 1950s or early 1960s [36] and its impact on national mortality rates, particularly for childhood leukaemias [37], has been observed since the late 1960s or early 1970s.

The average decline in the mortality rates from leukaemias for Western Europe in recent years under the age of 60 years was over 35% in both sexes, corresponding to the avoidance of over 7000 deaths per year. These declines have been greater among children but are evident throughout young adulthood and middle age, though progressively less marked.

Advancements in treatment and survival have been observed for acute myeloid leukaemia in patients under 60 years of age, but are less clear in elderly patients [38–40]. Some advantages for the newer chemotherapy regimens and bone marrow transplantations have been reported for myeloid leukaemia [41] and perhaps for chronic lymphocytic leukaemia too [42], but their impact on mortality rates on a population level remains undefined [43].

For adult leukaemias under 60 years of age, some decline in mortality was observed in most Eastern European countries too, averaging about 20% in this period. Most of these declines started from the late 1970s or early 1980s. This corresponds to the avoidance of approximately 1000 deaths from leukaemia per year, a figure which could be doubled if best available treatments were applied on a wider scale.

This again underlines the importance and urgency of the application of available knowledge on treatment of leukaemia in Eastern Europe, which may well lead to the avoidance of approximately 1000 further deaths per year.

6. Childhood tumours

Treatment of other childhood cancers also leaves ample scope for improvement. All Western European countries showed substantial declines in mortality over the last few decades, averaging over 50% in both sexes with an estimate of approximately 3000 deaths avoided. Favourable trends were observed in Eastern Europe, too, but the decline was only about 30%, corresponding to about 1000 deaths avoided per year.

These advances have largely been due to the development of multidrug chemotherapy protocols, and the introduction of various supportive measures to overcome toxicity, as well as the use of megavoltage radiation and improved diagnostic techniques. The declines observed in Western Europe are of the same order of magnitude as those registered in the USA over comparable time periods. The advances in Western Europe, however, came somewhat later and were systematically smaller (at least 10% for leukaemia and 20% for all childhood neoplasms) than in North America, indicating the delay in the adoption and implementation of efficacious techniques. Despite some difference in mortality registered by race and ethnicity, between 1960 and 1993, in fact, mortality from childhood leukaemia declined by 73% in North America, but only by 67% in Western Europe, and deaths from all childhood tumours by 61% in North America and 49% in Western Europe [37].

Almost certainly, therefore, there is scope for further reductions in childhood cancer mortality through more widespread adoption of the latest techniques. There is even more room for improvement in Eastern Europe, where approximately 500 further deaths from childhood cancer per year could be avoided.

At age 15–19 years, a different proportional composition of various neoplasms is observed, with a rise of testicular cancer in boys, of germ cell ovarian neoplasms in girls, and mostly of bone neoplasms in both sexes. None the less, mortality from all neoplasms, as well as from leukaemias, declined by almost 50% since the late 1960s, while in Eastern Europe some modest decline (about 20% in boys, 25% in girls) was observed only in the last 10 years, again reflecting the delayed and inadequate adoption of efficacious treatments for various cancers in Eastern Europe.

7. Testicular cancer

In Western Europe, mortality rates from testicular cancer have substantially declined over the last two decades, although the incidence of the disease has been rising. Rates fell on average by over 50% in the whole of Western Europe, implying the avoidance of approximately 800 deaths per year if the rates for the late 1950s were applied to the population structure of the early 1990s. The progress may well have been greater, since the incidence has been rising over the last few decades in several parts of the world. In Eastern Europe, indeed, where newer therapies have probably had less impact, mortality rates rose on average by approximately 60% and have only started to decline in the last few years [16].

Thus, the absolute advantage of newer therapies on testicular cancer mortality in Western Europe may well be substantially larger, with possibly almost 1000 deaths avoided per year. The delay or non-application of newer therapeutic approaches for testicular cancer in Eastern Europe has probably resulted in an excess of approximately 500 avoidable deaths per year. The importance of these figures is highlighted by the age distribution for testicular cancer, including seminomas and teratomas, i.e. the histotypes largely affected by the improved ther-

apy, which show an early peak in the third decade of life.

8. Breast cancer

Breast cancer is probably the tumour for which the most appreciable gains in survival have been made over the last few years through improved diagnosis and screening, as well as improved treatment, including adjuvant treatment for early stage breast cancer [15,35]. Screening at 2–3 year intervals between the ages of 50 years (and perhaps 45 years) and 70 years reduces cancer mortality by 25–30%.

The Early Breast Cancer Trialists' Collaborative Group [44,45] showed that some months of adjuvant polychemotherapy with cyclophosphamide (CMF) or an anthracycline-containing regimen increases breast cancer survival by 7–11% for women under the age of 50 years, and by 2–5% for those aged 50–69 years. Some years (up to 5) of adjuvant tamoxifen improves 10-year survival by approximately 11% for node-positive and 6% for node-negative neoplasms. There was also a substantial reduction of controlateral breast cancer cases, which led to the adoption of tamoxifen in the chemoprevention of breast cancer [46–49].

Tamoxifen is also effective in the prevention of invasive cancer in women with *in situ* ductal carcinoma of the breast [50]. Raloxifene and other selective oestrogen receptor modulators (SERMS) may also be beneficial, but their effects have not yet been precisely quantified in clinical trials.

Within the EU, the theoretical scope for rational screening and the widespread adoption of adjuvant treatment may correspond to 10 000 breast cancer deaths avoided per year, i.e. approximately 20% of the total deaths from the disease. Breast cancer mortality at age 35–64 years over the last few years has declined by less than 5% (from 43.0 to 41.9/100 000), so there is still ample room for improvement, even if only by adopting the optimal available approaches.

Although the advances in breast cancer management have been modest, the impact on reducing mortality could, at least in principle, be greater than for any other neoplasm.

9. Clinical research in colorectal and lung cancer

For other neoplasms, it is not yet possible to provide reliable estimates of the impact of therapeutic improvements on a population level. Consequently, indications for potential advancement in cancer therapy have to be based essentially on the results of clinical trials. In the sections that follow, the current status of clinical research on two major neoplasms, colorectal and lung cancer, will be reviewed. Other common cancers, such as stomach, liver, prostate, oesophagus and bladder, are not discussed in the absence of major current advancements registered in their treatment.

10. Colorectal cancer

Surgery is a very effective treatment for colorectal cancer when it is diagnosed early.

The therapy of advanced colorectal cancer has been centered for a long time on the use of 5-fluorouracil (5-FU), but the drug has only a modest response rate, with limited impact on survival [51]. Thus, during the past 45 years, innumerable studies have set out to improve the anticancer activity of 5-FU by clarifying its kinetics, metabolism and mechanism of action (for a review see Ref. [52]).

Based on experimental findings and empirical approaches, a large number of phase II and phase III clinical trials have been designed to answer questions related to the treatment of stage III colorectal cancers, whereas no adjuvant therapy in stage II is of substantial benefit [53–56]. Various routes of administration have been employed, besides the oral and, to deliver 5-FU as far as possible to the tumour or at the main metastases in the liver: bolus intravenous (i.v.), continuous infusion, hepatic artery infusion or portal vein infusion. Chronomodulation has been tested too, with different treatment schedules.

Favourable results have been obtained in terms of response rates or time to tumour progression with all these modalities. However, as the representative results in Table 2 show, when overall survival is considered the outcome is discouraging; the differences are small, even when they reach statistical significance. The absolute median overall survival is around 12 months with variability, depending on the schedule of treatment and the stage of the disease-ranging from 8 to 15 months; this represents an advantage over the 'best supportive care', for which the figure is between 5 and 7.5 months [57–59]. However, most of the studies were non-comparative, poorly controlled and with few patients, so any conclusion on the merits of the single treatment modalities remains doubtful.

Hopes were raised by technological advances which make it possible to pump drugs directly into the liver by hepatic artery infusion (HAI), but the results have been limited to an increase in response rate which has not translated into any significant gain in survival [60,61].

Another step in the effort to potentiate the action of 5-FU has involved the introduction of leucovorin (folinic acid) to ensure adequate intracellular concentrations of reduced folate to permit a tight bond between fluorodeoxyuridine monophosphate (the active metabolite of 5-FU) and thymidylate synthase [62–64]. Leucovorin

plus 5-FU has provided benefits over 5-FU alone in terms of remissions [65,66], but has not prolonged survival (11.5 months for 5-FU + leucovorin and 11 months for 5-FU alone), as established by the European Organization for Research and Treatment of Cancer (EORTC) meta-analysis on approximately 1400 patients [51,67]. Furthermore, high doses of leucovorin were not superior to conventional doses [67–69].

Other ways to modulate the action of 5-FU have been reviewed by Ardalan and colleagues [52] and Kamm and colleagues [70] and include the combination with methotrexate (with or without leucovorin) (see Table 2) or trimetrexate, N(phosphoacetyl)L-aspartate (PALA), with or without leucovorin. The results are not definitive, but there appears to be no dramatic change in the action of 5-FU. However, the various modalities of administering 5-FU have been claimed to produce less toxicity, and this awaits large controlled clinical trials.

New hopes for first-line treatment of colorectal cancers come from recent results with newer drugs. UFT is

Table 2
Advanced colorectal cancer: first-line treatment. Representative results of clinical trials expressed as median survival time

No. pts	Drug	Modality	Median survival (months)	Ref.
41	FUDR	HAI	13.8	[178]
	5-FU	PI	11.6	[178]
143	FUDR	HAI	15.4	[179]
	FUDR	PI	15.8	[179]
1219[a]	5-FU	CI	12.1	[180]
	5-FU	B	11.3	[180]
174	5-FU	CI	13.0	[181]
	5-FU	B	12.0	[181]
170	5-FU	CI	9.5	[182]
	5-FU	B	9.5	[182]
148	5-FU + MTX	–	12.0	[183]
	5-FU	–	12.0	[183]
117	5-FU + MTX	–	8.0	[184]
	5-FU + MTX	(+) LV	8.0	[184]
	5-FU	–	8.0	[184]
120[b]	Irinotecan	Different doses and cycles	11.8–12.1	[90]
162	5-FUDR	HAI	17.0	[185]
	5-FUDR	PI	12.0	[185]
61	5-FU	HAI	15.4	[186]
	5-FU	PI	13.5	[186]
	5-FU	PVI	15.0	[186]
348	5-FU	5-FU	14.2	[187]
	NCCTG Mayo Clinic	–	13.1	[187]
148	5-FU	–	11.0	[188]
	5-FU	H-LV	11.0	[188]
1381[a]	5-FU	–	11.5	[189]
	5-FU	–	11.0	[189]
101	5-FU	CI-H-LV	18.0	[190]
75	UFT	LV	13.5	[191]
38	UFT	LV	12.5	[192]
27	Oxaliplatin	–	13.0	[193]
25	Oxaliplatin	–	14.5	[194]
90	Oxaliplatin + 5 FU	LV (chronomodulation)	19.0	[89]
	Oxaliplatin	–	16.2	[76]
	Oxaliplatin + 5 FU	LV	14.7	[76]
439	Raltitrexed	–	10.1	[51,195]
	5-FU	(+) LV	10.2	[51,195]
427	Raltitrexed	–	9.7	[51,195]
	5-FU	(+) LV	12.7	[51,195]
495	Raltitrexed	–	10.9	[51,195]
	5-FU	(+) H-LV	12.3	[51,195]
667	Irinotecan + 5-FU	LV	14.4	[76]
	Irinotecan	–	12.6	[76]
	5-FU	LV	12.6	[76]

HAI, hepatic arterial infusion; PI, Peripheral infusion; CI, continuous infusion; UFT, uracil + tegafur; pts, patients; FUDR, fluorodeoxyuridine; MTX, methotrexate; B, bolus; LV, leucovorin factor (H = high dose); PVI, portal vein infusion; NGCTG Mayo Clinic: bolus 5 days every 3 weeks.

[a] Meta analysis.

[b] Pooled data.

a combination of uracil and tegafur, an orally active prodrug of 5-FU. Phase II trials with UFT and leucovorin have yielded results on survival in the range of those observed for 5-FU + leucovorin (see Table 2).

Irinotecan is a semisynthetic camptothecin analogue that inhibits topoisomerase I and is a prodrug for the active metabolite SN-38 [71,72]. Three phase II trials including about 120 patients showed a good rate of remissions (19–32%) and a worthwhile proportion of patients (32–55%) achieved stable disease, with median survival ranging from 11.8 to 12.1 months [73–75]. The toxicological profile of irinotecan does not overlap with that of 5-FU.

These results, obtained with the first drug offering efficacy equivalent to the current treatment with 5-FU, have raised the question of a possible synergism between irinotecan and 5-FU plus leucovorin. Data not yet published, but presented at the 1999 ASCO meeting [76], indicate a possible advantage of the combination over irinotecan alone; however, after 12 months of follow-up, the overall survival rate was 14.4 months, compared with 12.6 months for the single treatment.

Raltitrexed, a direct non-competitive inhibitor of thymidylate synthase [77,78] proved effective as monotherapy in three phase III clinical studies of over 1300 patients with advanced colorectal cancer [79,80]. However, raltitrexed can be considered at best equivalent to 5-FU although, at the 1999 ASCO meeting [76], more deaths related to the raltitrexed treatment (6%) were reported than with 5-FU (1%), with or without leucovorin. The toxicological profile of raltitrexed differs in some respects, causing less leucopenia and more hepatic toxicity than 5-FU [79].

Oxaliplatin is a new third-generation platinum complex which, unlike cisplatin [81–83] or carboplatin [84–86], has been found to be effective in untreated patients. The overall survival in phase II studies was not appreciably different from 5-FU treatment (Tables 2 and 3) [87,88]. The combination of oxaliplatin with chronomodulated 5-FU and leucovorin gave a median survival of 19 months [89]. However, synergism between oxaliplatin and 5-FU was questioned at the 1999 ASCO Meeting [76].

Alternative treatments are now available for second-line therapy (Table 3) when patients are becoming refractory or are progressing after 5-FU treatment. Under these conditions, irinotecan has proved better than best supportive care [90,91], with a median survival of 8.2–10.8 months, as against 6.8 months. Oxaliplatin is the other drug showing activity in second-line therapy, either alone [92] or with 5-FU [93].

On the whole, the therapy of advanced colorectal cancer is still unsatisfactory, although some newer drugs—oxaliplatin, irinotecan and raltitrexed—offer alternatives to 5FU, with new combinations taking advantage of the different toxicity profiles. Much remains to be done in advanced colorectal cancer to achieve a substantial improvement of survival, which at present does not exceed 12–18 months under the best conditions.

11. Lung cancer

Lung cancer is the most common cause of cancer deaths in the US and in Europe, with an age-standardised rate of approximately 60 deaths per 100 000 males per year [16]. In the US, there are approximately 170 000 new cases every year and 160 000 deaths per year, figures which indicate the poor results with available therapies [94]. The importance of lung cancer is summarised by noting that it accounts for 28% of all cancer deaths, exceeding the deaths from breast, prostate, colorectal and ovarian cancers combined [94].

For treatment purposes, lung cancers can be classified as small-cell (SCLC) and non-small cell (NSCLC) types, making up, respectively, 15–25 and 75–80% of all lung cancers [94,95].

Table 3
Second-line treatment of colorectal cancer

No. Pts	Drug	Modality	Median survival (months)	Ref.
64	Irinotecan		10.6	[90]
429[a]	Irinotecan	Different doses and cycles	8.3–10.4	[90]
189	Irinotecan	Different doses and cycles	9.2	[196]
90	Best supportive case	–	6.8	[196]
133	Irinotecan	–	10.8	[197]
134	5-FU	CI	8.5	[197]
57	5-FU	CI + LV	8.0	[198]
69	5-FU	CI + LV	9.0	[199]
55	Oxaliplatin	–	8.2	[200]
29	Oxaliplatin	–	10.0	[92]
46	Oxaliplatin + 5-FU	LV	17.0	[93]

CL, continuous infusion; LV, leucovorin factor; pts, patients.
[a] Pooled data.

11.1. Small-cell lung cancer

This cancer causes approximately 35 000 deaths per year the US alone [96]. Patients with limited disease (LD) should be given local radiotherapy [97] in combination with chemotherapy according to recently reviewed modalities [98]. However, controlled trials have not convincingly demonstrated the utility of this combination when the chemotherapy consisted of cisplatin or carboplatin + etoposide [99] or cyclophosphamide, doxorubicin and etoposide [100].

Combinations of i.v. cisplatin + etoposide or cyclophosphamide + doxorubicin + vincristine gave better results than cycles of oral etoposide in terms of survival. The difference, however, levelled off at one year (13% survivors in the i.v. arm and 11% in the oral arm) [101]; the quality of life and symptom control were better in the oral arm.

Increasing the doses of etoposide + cisplatin (PE) [102] and cyclophosphamide + doxorubicin + vincristine (CAV) [103] did not yield any survival benefit, and only gave increased toxicity.

In several studies, ifosfamide was substituted for cyclophosphamide in combinations with cisplatin and oral etoposide (PE). In one randomised trial, VIP was superior to PE [104]. However, there are no comparisons of VIP and cyclophosphamide + doxorubicin + vincristine (CAV).

Alternating regimens were tested in the hope of overcoming resistance; in several trials PE or CAV were compared with alternating PE/CAV (Table 4). In two trials, there was a small gain (1 or 2 months) in survival with the alternating regimen [105,106], but in a third trial [107] there was no difference.

Other studies compared weekly and intermittent therapy. Again, there was no difference in survival [108–110]. Similarly, increasing the dose of etoposide only in the PE regimen did not improve survival, but aggravated the haematological toxicity [111].

The duration of chemotherapy is another open question. Is it useful to continue therapy in patients showing remission or stabilisation? Several trials have tried to answer this, but their results were not encouraging because maintenance therapy did not have any major impact on survival or on quality of life [112–115].

Similar conclusions were reached in a qualitative overview [116], which analysed the results of 13 randomised clinical trials and objected to their poor quality. This analysis was confirmed by another review of 15 trials [117].

At the present time, the treatment for limited-disease SCLC is platinum-based—is carboplatin better?—com-

Table 4
Selected trials for the treatment of advanced small-cell lung cancer

No. pts	Drug(s)	Median survival (months)	Ref.
32	Paclitaxel	6.4	[201]
37	Paclitaxel + GCSF	6.7	[121]
46	Docetaxel	9.0	[202]
12	Paclitaxel + cisplatin + etoposide	10.0	[124]
26	Paclitaxel + cisplatin + etoposide	14.4	[125]
87	Topotecan	7.0	[203]
48	Topotecan	10.0	[204]
15	Irinotecan	6.0	[205]
31	Irinotecan	4.5	[130]
23	Vinorelbine	8.0	[206]
43	Vinorelbine + carboplatin	8.4	[140]
84	Cisplatin + etoposide	7.3	[207]
148	Cisplatin + etoposide	8.6	[107]
87	Cisplatin + etoposide + ifosfamide	9.1	[207]
35	Carboplatin + etoposide + ifosfamide	9.0	[208]
72	Cisplatin + etoposide[a]	12.5	[209]
72	Carboplatin + etoposide[a]	11.8	[209]
101	(CAV) cyclophosphamide + doxorubicin + vincristine	8.0	[103]
44	Cisplatin + etoposide	11.4	[102]
148	Cisplatin + etoposide[a]	24.0	[106]
288	CAV	9.9	[106]
	Cisplatin + etoposide (PE)	9.9	[106]
	CAV/PE alternating	11.8	[106]
437	CAV	8.3	[107]
	PE	8.6	[107]
	CAV/PE alternating	8.1	[107]

GCSF, granulocyte colony stimulating factor.
[a] Limited disease.

bined with etoposide, or else the CAV regimen. Results are less favourable in extensive disease, although recently the CODE regimen (cisplatin + vincristine + doxorubicin + etoposide) achieved remarkable survival gains (median 13 months) in a phase II [118] and a phase III trial [119] at the expense, however, of excessive early mortality.

Several new drugs have appeared recently, although their utilisation is still limited and many questions remain.

Paclitaxel and docetaxel are two compounds with a taxane structure that bind tubulin [120]. A 68% response rate was reported for paclitaxel in patients with previously untreated SCLC [121], but the median survival did not exceed 6.5 months. Preliminary studies combining paclitaxel with cisplatin or carboplatin under different schedules also failed to prolong survival [122–126]. Much less data are available for docetaxel, which achieved an 18% response rate in previously treated patients [127].

Irinotecan and topotecan are topoisomerase I inhibitors with demonstrated efficacy in untreated and previously treated patients. Irinotecan gives potentially interesting response rates, but survival was short (4.5–6.0 months) [128–130]. Similar data were obtained in combination with etoposide or cisplatin [131].

Phase II studies for topotecan (for review see Ref. [132]) in second-line treatment were encouraging [133], but a randomised trial in comparison with the classical CAV regimen did not show any advantage [134]. For first-line therapy, 40% responses, median survival of 10 months and a 1-year survival of 39% [135] have been reported.

Gemcitabine is an analogue of cytosine arabinoside (ARA-C) which has been tested in combination with cisplatin, but no results are yet available. Vinorelbine is one of the vinca alkaloids showing activity as a single agent, although the results were not particularly promising [136–139]. The combination with carboplatin in extensive disease SCLC gave a median survival of 8.4 months [140].

The introduction of autologous bone marrow therapy in combination with high-dose chemotherapy as an initial treatment has allowed a high rate of complete responses, although overall survival was no different from conventional multicycle regimens (summarised in Ref. [141]). Results of a number of trials in advanced SCLC are summarised in Table 4.

11.2. Non-small cell lung cancer

More than 75% of lung cancer patients have non-small cell lung cancer (NSCLC) which comprises four forms: adenocarcinoma, squamous cells, large cells and bronchoalveolar. The majority of patients show locally advanced or metastatic disease and only 20% are candidates for curative surgical resection [142]. The overall five-year survival for all patients is approximately 13% [143]. Chemotherapy is considered useful in extensive disease [144] on the basis of two large meta-analyses [145,146], one of them [146] including 52 randomised clinical trials. The survival benefit is statistically significant compared with best supportive care, with an almost doubling of the 1-year survival rate. However, chemotherapy is detrimental in combination with surgery (5% less survival at 5 years) or in combination with radical radiotherapy (4% less survival at 2 years) [146].

Some improvement has been achieved with new drugs combined with cisplatin or carboplatin. For instance, the combination of gemcitabine + cisplatin is better than cisplatin alone [147], but is equivalent to the combination mitomycin + ifosfamide + cisplatin in terms of survival. Carboplatin + paclitaxel is another well-tolerated combination, but median survival does not exceed 9.5 months [148]. The combination of carboplatin + paclitaxel has been adopted as the present reference regimen on the basis of two phase III studies [149,150], more because of its relatively good tolerability than for any substantial survival difference over cisplatin + etoposide or teniposide. The triple combination paclitaxel + carboplatin + gemcitabine gave a better objective response rate, but clinically no significant difference in survival from paclitaxel + carboplatin [151]. However, randomised trials are needed for confirmation.

Other triple combinations are gemcitabine + vinorelbine + cisplatin [152–154] and gemcitabine + ifosfamide + cisplatin [155,156], which have produced encouraging results, but need to be confirmed by phase III studies.

Amifostine (WR 2721) is a cytoprotective agent that can reduce the toxic effects of chemotherapy and radiation [157–159]. Cisplatin- or carboplatin-based regimens have been used in combination with amifostine, giving advantages in terms of toxicity, with a median survival of 17 months for the combination with cisplatin + vinblastine in one study [160] and 14 months in another [161].

Irinotecan has also been tried in NSCLC. As a single agent in untreated patients, there were only 15–34% partial responses [162–164], and, in previously treated patients, no responses were observed [162]. When irinotecan was combined with cisplatin, the response rates were still only partial and ranged between 31% [165] and 55% [166–168]. Irinotecan has also been combined with etoposide [169], but the results were no better than with current regimens.

For these combinations, and the possibility of using irinotecan as a radiosensitiser [170], randomised clinical trials of the necessary size and with appropriate comparative arms are needed. The results of a number of trials in advanced NSCLC are reported in Table 5.

In summary, chemotherapy is somewhat more active in SCLC than NSCLC, but the results are still limited.

Table 5
Selected trials for the treatment of advanced NSCLC

No. pts	Drug(s)	Median survival (months)	Ref.
218	Cisplatin	6.0	[210]
214	Cisplatin + vinorelbine	8.1	[210]
154	Cisplatin	7.4	[211]
155	Cisplatin + gemcitabine	9.0	[211]
205	Cisplatin	8.2	[212]
202	Cisplatin + paclitaxel	8.1	[212]
119	Vinorelbine	7.4	[213]
121	Vinorelbine + cisplatin	7.5	[213]
188	Vinorelbine	7.1	[214]
182	Vinorelbine + cisplatin (high dose)	9.3	[214]
72	Gemcitabine	5.8	[215]
75	Cisplatin + etoposide	6.7	[215]
27	Gemcitabine	8.2	[216]
25	Cisplatin + etoposide	11.1	[216]
155	Cisplatin + paclitaxel	8.2	[217]
157	Cisplatin + teniposide	8.2	[217]
155	Gemcitabine + cisplatin	8.2	[218]
152	Cisplatin + mitomycin C + ifosfamide	9.1	[218]
77	Carboplatin + paclitaxel + gemicitabine	9.4	[219]
52	Carboplatin + paclitaxel	7.2	[220]
100	Carboplatin + paclitaxel	8.0	[221]
38	Carboplatin + paclitaxel + gemcitabine	9.4	[148]
20	Amifostine + carboplatin	14.0	[161]
20	Carboplatin	9.0	[161]

NSCLC, non-small cell lung cancer.

Even if there is some gain in terms of response rate with the various regimens, survival is still very short and certainly unsatisfactory considering the variety of drugs available.

12. Estimated effects of newer therapies on cancer mortality

The cancer deaths avoided through the development and implementation of newer therapies amount to 2–3% of all cancer deaths registered per year in Europe [17]. The corresponding public health and social impact, however, is much larger than this crude percentage since most of these avoided deaths are among young and middle-aged people so their impact is considerably greater in terms of years of life saved. For a summary tabulation, changes in the EU between 1985 and 1994 in age-standardised mortality at age 35–64 years for most common cancer sites are given in Table 6, together with longer term trends since 1970.

It is difficult to estimate the potential impact of therapies for several cancer sites, including some of those in Table 6. Mortality from cancers of the stomach and of the cervix uteri declined substantially, but these favourable trends cannot be attributed—except for a very small part—to therapy, since modern surgery for these neoplasms was already available in the 1950s, nor to better control of identified risk factors, although the fall in cervical cancer mortality is largely due to screening [18]. It is none the less likely that some progress is concealed in the trends in mortality from a few common

Table 6
Changes in age-standardised[a] and sex-standardised mortality at age 35–64 years from selected neoplasms in the European Union, 1960–1994

Type of cancer	Males, death rates			Change in rates, 1985–1994	Females, death rates			Change in rate, 1985–1994
	1970–1974	1985–1989	1990–1994		1970–1974	1985–1989	1990–1994	
Lung	68.7	73.7	68.3	−7.3	10.4	13.5	14.3	+5.9
Colorectum	20.4	21.6	21.4	−0.9	17.2	15.9	14.7	−7.5
Stomach	28.0	16.6	13.9	−16.3	12.2	7.3	6.3	−13.7
Breast	–	–	–	–	39.5	43.0	41.9	−2.6
Prostate	5.1	5.8	5.9	+1.7	–	–	–	–
Leukaemias	6.6	6.1	5.6	−8.2	4.8	4.3	3.9	−9.3

[a] On the world standard population.

cancers, particularly breast. Even if limited in terms of the percentage decrease in mortality, this would have a major public health impact on account of the high incidence of these tumours.

For several reasons, therefore, the estimates given in this review should be taken as a lower limit of the impact of the progress achieved by anticancer drugs in Europe. This must not, however, eclipse the second major message emerging from this report, i.e. that there is appreciable scope for further improvement in cancer treatment in Europe through a more widespread and rational application of currently available therapies.

The present review cannot adequately address the progress that has been made in surgery, together with the related advancements in anaesthesiology and infection control since the 1950s, which have been responsible for substantial improvements in the survival of patients with several common solid neoplasms, including colorectal, breast, cervix and corpus uteri, prostate, etc., and, to a smaller degree, stomach, the upper digestive tract and lung [9,10].

Likewise, this paper cannot consider in detail the advances in radiotherapy, which have substantially contributed to the treatment of acute leukaemia, Hodgkin's disease, cervical and uterine as well as breast cancer [8]. Together with the progress in cancer control, there have also been, however, major side-effects resulting from radiotherapy. Thus, adjuvant irradiation for breast cancer has significantly reduced breast cancer recurrence and death, but not the total mortality following a concomitant increase in cardiac morbidity and mortality due to irradiation [9,171]. Modern radiotherapy techniques may reduce the excess cardiovascular morbidity, but the evidence at present remains controversial.

13. New anticancer drugs approved in Europe by EMEA (1995–1999)

The development of new anticancer drugs for the period January 1995–June 1999 can be evaluated by examining the European Public Assessment Reports (EPAR) and the Summaries of Product Characteristics (SPC) produced by the Committee for Proprietary Medicinal Products (CPMP), the scientific body of the EMEA which advises the European Commission on issuing drug marketing authorisations.

Docetaxel, a derivative of paclitaxel, has cytotoxic activity and is indicated as monotherapy for the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic therapy; it was approved on 27 November 1995. Previous chemotherapy should have included an anthracycline or an alkylating agent.

Docetaxel was approved, under exceptional circumstances, on the basis of six phase II studies concerning a total of 117 previously untreated patients and 111 previous treated patients. Complete response was observed in 4.4 and 7.3%, respectively, in alkylating agent-resistant and anthracycline-refractory patients, with a median duration of response of 27 and 28 weeks.

Two randomised phase III comparative studies followed. In alkylating-failure patients, docetaxel was compared with doxorubicin: no difference was observed in the overall survival time (15 months for docetaxel versus 14 months for doxorubicin). In anthracycline-failure patients, docetaxel was compared with mitomycin C + vinblastine, with an overall survival of 11 and 9 months.

Toremifene, an anti-oestrogenic drug, indicated for first-line treatment of hormone-dependent metastatic breast cancer in post-menopausal patients, was approved on 14 February 1996. Toremifene is not recommended for patients with oestrogen-receptor-negative tumours. Toremifene was approved on the basis of phase III studies including a total of 1869 post-menopausal women with advanced metastatic or disseminated breast cancer, in comparison with tamoxifen. The efficacy and the adverse effect profiles were not different, and toremifene 60 mg/day was therefore considered equivalent to tamoxifen 40 mg/day.

Doxorubicin hydrocloride inglobed in liposomes, a known anthracycline antitumoral drug, was approved on 21 June 1996 for a new indication, i.e. treatment of Kaposi's sarcoma in patients with AIDS. Doxorubicin was approved on the basis of two uncontrolled open pivotal studies. Complete responses were 6.3% in one study and zero in the other, but with symptomatic benefits. A prospectively randomised study in comparison with doxorubicin + bleomycin + vincristine did not show any difference, with a median duration of response of 90 days for doxorubicin-liposomes and 92 days for the combination chemotherapy.

Topotecan, a topoisomerase I inhibitor, indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy, was approved on 12 November 1996. Topotecan was approved on the basis of phase II/III studies: 235 patients previously treated with a platinum-based regimen were randomised to topotecan or paclitaxel; median survival was 62 and 53 weeks, respectively. Three additional open label, non-comparative phase II studies gave results similar to the phase III trial.

Rituximab, a chimeric mouse/human monoclonal antibody which binds to the antigen CD20 located on the surface of B-lymphocytes, indicated for patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy, was approved on 2 June 1998. The approval was based on two phase II clinical trials involving 203 patients, showing 48% complete (6%) and partial (42%) responses, an efficacy considered at

least similar to that obtainable in similar patients with cladribine or fludarabine. Rituximab showed a better toxicity profile.

Temozolomide, a prodrug for a known cytotoxic alkylating agent, monomethyltriazenoimidazole carboxamide (MTIC), indicated for the treatment of glioblastoma multiforme showing recurrence or progression after standard therapy, was approved on 20 January 1999. The approval was based on two phase II studies for a total of 338 patients. One of these (210 patients) made a comparison with procarbazine, a drug of doubtful efficacy for this indication. No complete responses were observed, and the median overall survival rates were 7.3 and 5.7 months, respectively, for temozolomide and procarbazine. It was suggested that temozolomide gave a better quality of life.

Tasonermin, a non-glycosylated protein belonging to the tumour necrosis factor alpha (TNF α) family, with both cytotoxic and immunomodulatory properties, indicated as adjuvant therapy for subsequent removal of the tumour so as to avoid or delay amputation, or in the palliative setting, for unresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion, was approved on 13 April 1999. The approval was based on phase II studies. Since there was no comparison with melphalan, the only positive efficacy finding was a comparison with historical data.

Paclitaxel, a known cytotoxic agent, indicated for the treatment of advanced AIDS-related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy, was approved on 19 July 1999. The approval was based on a single non-comparative study in 107 patients with advanced Kaposi's sarcoma, previously treated with systemic therapy (63 patients considered resistant to liposomal anthracyclines). Complete responses were 3.7% and partial responses 52.3%. No comparison is possible with other treatments.

The approval of new drugs in Europe does not justify much optimism in terms of real progress in cancer therapy. Nevertheless, more drugs are now available, particularly for patients who have become resistant to previous chemotherapy. The approval of new drugs offers new possibilities in terms of combined treatments or modalities. However, there is considerable uncertainty about the real value of new drugs because of the poor quality of the trials submitted. In general, these are not well controlled and have no appropriate comparisons with the best available treatment. Even when there is equivalence, it is not clear what kind of differences could have been actually observed in the trials.

The new drugs on the whole do not offer proven advantages, and their approval does not always respect the principles of evidence-based medicine. What is instead significant is the difference in price of the new drugs compared with the existing ones (see Table 7).

Table 7
Prices of some anticancer agents (in Euro)

Drug	Package	€
Tamoxifen	20 mg×30	18.8
Toremifene	60 mg×30	36.73
Procarbazine	50 mg×50	8.16
Temozolamide		1945.80
Doxorubicin	50 mg	92.92
Doxorubicin in liposomes	20 mg	402.89
Paclitaxel	100 mg	582.75
Docetaxel	80 mg	1250.92
Topotecan	4 mg	1392.05
Irinotecan	100 mg	170.45

Prices as of December, 1999.

Clearly, there is a need for better evaluation of the new drugs to avoid uncertainty in their efficacy and safety, and so as not to put an undue financial burden on the health services and on patients. The costs of cure for colon cancer patients in the early 1990s in the USA has been estimated around 30 000 USD, and that of several other common neoplasms (i.e. lung, prostate, breast, leukaemias) between 25 and 40 000 USD [1,172].

14. Concluding remarks

There is certainly a major gap between the efforts of cancer research and the practical results achieved. Despite advances in prevention and early diagnosis, only 2–3% of advanced cancers can be cured with today's therapies. With the notable exceptions of childhood lymphoblastic leukaemia, lymphomas and cancer of the testicles, the treatment of the most common solid tumours gives only partial results. As noted in other sections of this review, for lung and colorectal cancers—two of the most frequent tumours—there has been only a slight gain in survival despite an array of new drugs, new combinations and different schedules.

The short to medium-term outlook is not optimistic if one looks at the so-called 'new' drugs approved by the American and European regulatory authorities. Why is this so? The problem is that difficulties intrinsic to the cancer cells limit the efficacy of treatment. The heterogeneity of cancer cells in the same tumour is the main reason for the differences in sensitivity to anticancer drugs; genetic instability is at least one of the reasons for the development of resistance; poor vascularisation makes it difficult for any chemotherapeutic or immunological treatment to kill a worthwhile majority of cancer cells. In addition, the similarities between cancer and proliferating normal cells limits how much treatment can be applied because of toxicity; then too, the cancer cells' ability to disseminate and metastasise makes it difficult to reach those cells wherever they are.

Looking at the promises of the past, there are grounds for discouragement; the present, however, looks less bleak because for the first time in decades, progress has been made in understanding the biological processes involved in the proliferation, detachment, transport, invasion and homing of cancer cells. The molecular biology of the many factors that stimulate or inhibit these processes is becoming clearer. In turn, these molecules offer suitable targets for chemicals rationally designed to have anticancer activity.

Multiple new pathways to attack cancer are therefore available. Each approach may play a different role. For instance, precancerous lesions may be the targets of chemoprevention strategies to reduce or avoid gene modifications induced by carcinogens in our environment [173,174]. Inhibition of angiogenesis and vascular targeting have recently received a lot of attention because this approach is not aimed directly at cancer cells, but at the vessels which bring essential nutrients to those cells, and enable the cells to disseminate toward other organs.

Counteracting resistance, if successfull, will be a major step forward in second- and third-line therapy when available drugs have failed to arrest the progression of the tumour. In this respect, the search for cytotoxic agents that do not create cross-resistance with current drugs must continue, taking advantage of the knowledge available on the mechanisms of resistance. Current therapies could be optimised with the development of pharmacogenomics [175], as exemplified by individualisation of drug dosages in the treatment of acute lymphoblastic leukaemia (ALL) [176]. Anticancer vaccines will probably play a major role in eradicating the residual cancer cells left after successful surgery following early detection.

Gene therapy is a theoretical approach for the time being, although several trials are in progress; in the presence of significant results, there will be an explosion of possible approaches considering the huge potential of gene transfer for affecting cancer proliferation, dissemination, angiogenesis, resistance and antigenicity.

The hope is to be able to combine the different approaches with current therapies, or to use them in sequence in order to prevent tumour progression, even if it is not possible to obtain a cure.

Therefore research, together with prevention, is still essential to improve our knowledge on cancer and to capitalise on progress made, as well as to obtain practical results. In the future, there will probably be an array of potential drugs, calling for even more stringent criteria in selecting drugs for clinical trials. Criteria for approving new drugs will have to be more severe so as to avoid too many drugs with similar activity, but ever-higher prices, flooding the market. The economical and social implications of new strategies in cancer treatment are still unclear, for developed and, even more, for developing countries, where as many as 20 million new cancer cases per year will arise over the next two decades [177].

Finally, the public must be made aware of the difficulties inherent in the task of curing cancer, in order to avoid discouraging patients and their families and to ensure that a lack of confidence in cancer research is not created.

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