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Overview

The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies

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ABSTRACT:
Aims: The debate on the funding and availability of cytotoxic drugs raises questions about the contribution of curative or adjuvant cytotoxic chemotherapy to survival in adult cancer patients.
Materials and methods: We undertook a literature search for randomised clinical trials reporting a 5-year survival benefit attributable solely to cytotoxic chemotherapy in adult malignancies. The total number of newly diagnosed cancer patients for 22 major adult malignancies was determined from cancer registry data in Australia and from the Surveillance Epidemiology and End Results data in the USA for 1998. For each malignancy, the absolute number to benefit was the product of (a) the total number of persons with that malignancy; (b) the proportion or subgroup(s) of that malignancy showing a benefit; and (c) the percentage increase in 5-year survival due solely to cytotoxic chemotherapy. The overall contribution was the sum total of the absolute numbers showing a 5-year survival benefit expressed as a percentage of the total number for the 22 malignancies.
Results: The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1% in the USA.
Conclusion: As the 5-year relative survival rate for cancer in Australia is now over 60%, it is clear that cytotoxic chemotherapy only makes a minor contribution to cancer survival. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required. Morgan, G. *et al*. (2004). *Clinical Oncology* **16,** 549–560

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Introduction

In adults, cytotoxic chemotherapy became established in the 1970s as a curative treatment in advanced Hodgkin's disease [1], non-Hodgkin's lymphoma [2], teratoma of testis [3] and as an adjuvant treatment for early breast cancer [4].

The initial results suggested the potential use of cytotoxic chemotherapy as a definitive treatment or as an adjuvant therapy in asymptomatic patients with the aim of improving survival. However, as stated by Braverman [5] and others [6–8], the early gains in a few tumour sites have not been seen in the more common cancers. For most patients, the use of cytotoxic chemotherapy is for the palliation of symptoms and to improve quality of life [9], with prolongation of survival being a less important outcome.

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Some practitioners still remain optimistic that cytotoxic chemotherapy will significantly improve cancer survival [10]. However, despite the use of new and expensive single and combination drugs to improve response rates and other agents to allow for dose escalation, there has been no change in some of the regimens used, and there has been little impact from the use of newer regimens. Examples are non-Hodgkin's lymphoma [11] and ovarian cancer [12], in which cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) and platinum, respectively, (introduced over 20 years ago) are still the 'gold standard' treatment. Similarly, in lung cancer, the median survival has increased by only 2 months during the same time period [13,14], and an overall survival benefit of less than 5% has been achieved in the adjuvant treatment of breast, colon, and head and neck cancers [15–17].

The recent debate on funding of new cytotoxic drugs [18–20] has highlighted the lack of agreement between medical oncologists and funding bodies on the current and

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future value of cytotoxic chemotherapy in cancer management.

In 1986, Kearsley [6] estimated that the contribution of chemotherapy to overall survival in the USA was 4.3%. By reassessing the contribution of definitive and adjuvant cytotoxic chemotherapy to 5-year survival in adult malignancies, we sought to update the estimate in order to provide a more rational basis for the current debate on funding and availability.

Methods

We undertook a literature search for randomised-controlled trials (RCTs) that reported a statistically significant increase in 5-year survival due solely to cytotoxic chemotherapy in adult malignancies (defined as 20 years of age or over). The search period was from 1 January 1990 until 1 January 2004. We searched Medline, Cancerlit and Embase to identify RCTs for each neoplasm using the MeSH headings of chemotherapy, radiotherapy and combined modality treatment. We used the Cochrane Collaboration and the Cochrane Cancer Library to identify meta-analyses and systematic reviews reporting the pooled results of RCTs. We also hand searched reference lists in published papers and other relevant articles.

We accepted the results of the RCTs, meta-analyses or systematic reviews as reported, and did not critically review the data further. As a measure of long-term survival and possible cure, 5-year survival data were used. When 5-year data were not available, shorter survival times were used, provided the outcome reported was statistically significant. We did not attempt to evaluate the effect on cancer outcomes of hormones, immunotherapy, antibodies, tumour vaccines, gene therapy or other novel techniques. Similarly, we did not evaluate the use of cytotoxic chemotherapy for the palliation or non-curative treatment of malignancy, as an impact on 5-year survival was unlikely.

The preferred source of evidence was either a systematic review or a meta-analysis of the RCTs for that malignancy. An RCT could take precedence over a systematic review or meta-analysis, but only when the RCT was from a reputable trials group, more recent than the systematic review or meta-analysis, randomised approximately 1000 patients, and the results were of such a magnitude that data from a previous analysis was clearly inferior.

For each malignancy, the absolute number of individuals obtaining an improvement in 5-year survival as a result of chemotherapy was the product of the number of newly diagnosed cancer patients aged over 20 years with that malignancy, the proportion or subgroup(s) showing a benefit, and the percentage increase in 5-year survival resulting solely from cytotoxic chemotherapy.

For the 22 major malignancies evaluated (Tables 1 and 2), the number of individuals with cancer aged 20 years and over in 1998 were calculated, using the cancer incidence data for Australia from the Australian Institute of Health and Welfare (AIHW) [21] (http://www.aihw.gov.au) and the Surveillance, Epidemiology, and End Results (SEER) data for the USA [22] for 1998.

Malignancies with small total numbers, such as gall bladder, pleura, eye, bone, penis and placenta were excluded. Acute and chronic leukaemia ($n = 1647$ or 2% of total) were not included because of the difficultly in defining outcomes according to FAB (French–American–British) classification and the different outcomes for children and adults. Also, these patients are usually cared for by clinical haematologists rather than medical oncologists. For Australia, the 22 malignancies evaluated were 90% of the total number of newly diagnosed cancer patients for 1998.

In most instances, the contribution to 5-year survival applied to subgroups that varied according to histology, stage, nodal involvement or menopausal status. The size of these subgroups was obtained from data on the distribution of stage in the South Australian Cancer Registry for 1998 [23], from the SEER data for 1998 [22] or from patterns of care studies [24].

The percentage increase in 5-year survival with cytotoxic chemotherapy for the malignancy as a whole or for the subgroup was identified by the literature search as detailed above. Each malignancy was evaluated separately and the absolute number of people to benefit was established. The overall contribution of cytotoxic chemotherapy to 5-year survival was the sum total of the absolute numbers to benefit expressed as a percentage of the total number of cancer patients in the 22 malignancies evaluated.

To establish the general applicability of the data, the contribution to 5-year survival was calculated separately for Australia and the USA. Where assumptions were made, we erred on the side of over-estimating the benefit.

Results

Results are arranged in ICD-9 groupings and are presented in Tables 1 and 2.

Head and Neck Cancer

ICD-9: 140–149, 160, 161; incidence: 2486 (Australia), 5139 (SEER).

Most people with head and neck cancer are treated for cure with radical surgery, radiotherapy, or a combination of both. Three meta-analyses were identified [25–27], which did not show any benefit from adding chemotherapy to radical radiotherapy with or without surgery. A subgroup analysis of a more recent meta-analysis showed a 4% overall improvement in survival with concurrent radiotherapy and chemotherapy [17]. The improvement was restricted to people with extensive disease, and this has been shown separately in advanced glottic cancer [28] and cancer of nasopharynx [29]. The benefit from chemotherapy will only be seen for those with stage III and IV disease. In 1998, this was 63% of the total in Australia and 47% of the total in the USA.

Table 1 − Impact of cytotoxic chemotherapy on 5-year survival in Australian adults

Malignancy	ICD-9	Number of cancers in people aged >20 years*	Absolute number of 5-year survivors due to chemotherapy†	Percentage 5-year survivors due to chemotherapy‡
Head and neck	140−149, 160, 161	2486	63	2.5
Oesophagus	150	1003	54	4.8
Stomach	151	1904	13	0.7
Colon	153	7243	128	1.8
Rectum	154	4036	218	5.4
Pancreas	157	1728	–	–
Lung	162	7792	118	1.5
Soft tissue sarcoma	171	665	–	–
Melanoma of skin	172	7811	–	–
Breast	174	10 661	164	1.5
Uterus	179 + 182	1399	–	–
Cervix	180	867	104	12
Ovary	183	1207	105	8.7
Prostate	185	9869	–	–
Testis	186	529	221	41.8
Bladder	188	2802	–	–
Kidney	189	2176	–	–
Brain	191	1116	55	4.9
Unknown primary site	195−199	3161	–	–
Non-Hodgkin's lymphoma	200 + 202	3145	331	10.5
Hodgkin's disease	201	341	122	35.8
Multiple myeloma	203	1023	–	–
Total		72 903§	1690	2.3%

*Numbers from Ref. [21].
†Absolute numbers (see text).
‡% for individual malignancy.
§Total for Australia 1998 = 80 864 people.

Number benefiting from chemotherapy

Australia: 2486 (incidence) × 63% (subgroup) × 4% (benefit from chemotherapy) = 63 people (2.5%); SEER: 5139 (incidence) × 47% (subgroup) × 4% (benefit from chemotherapy) = 97 persons (1.9%).

Oesophageal Cancer

ICD-9: 150; incidence: 1003 (Australia), 1521 (SEER).

The survival for oesophageal cancer is less than 10% at 5 years [30]. For every 100 newly diagnosed patients, one-third has metastatic disease (M1) at presentation ($n = 33$). In the remainder ($n = 67$), only 40% ($n = 26$) are medically operable, and only 80% of these will have a curative procedure ($n = 21$). Those who do not have an operation ($n = 67 - 21 = 46$) are suitable for treatment by radiotherapy or a combination of chemotherapy and radiotherapy.

In a Cochrane review reporting seven RCTs and 1653 patients [31], preoperative chemotherapy in resectable thoracic cancers was not shown to have a role, but an MRC trial [32] and a recent meta-analysis [33] has confirmed a benefit for preoperative chemotherapy.

A further Cochrane review [34] of combined chemotherapy and radiotherapy compared with radiotherapy alone for oesophageal cancer showed a significant absolute improvement in overall survival at 1 and 2 years for combined chemotherapy and radiotherapy of 9% and 8% respectively, and a 5% absolute reduction in local failure. It can be concluded that, when a non-operative approach was selected, then concomitant chemotherapy and radiotherapy were superior to radiotherapy alone. Chemotherapy, therefore, has a curative role in all patients except those who are M1 at presentation.

Number benefiting from chemotherapy

Australia: 1003 (incidence) × 67% (subgroup) × 8% (benefit from chemotherapy) = 54 people [4.8%]; SEER: 1521 × 67% × 8% = 82 people [4.9%]. This is likely to be an overestimate as data were only available for 2-year follow-up.

Stomach Cancer

ICD-9: 151; incidence: 1904 (Australia), 3001 (SEER).

Stomach cancer has a 22.6−24.8% 5-year survival [30], with surgery being the only established curative procedure. Meta-analyses in 1993 [35] and 1999 [36] suggested that adjuvant chemotherapy might produce a small survival benefit of borderline significance in curatively resected

Table 2 – Impact of cytotoxic chemotherapy on 5-year survival in American adults

Malignancy	ICD-9	Number of cancers in people aged >20 years*	Absolute number of 5-year survivors due to chemotherapy†	Percentage 5-year survivors due to chemotherapy‡
Head and neck	140–149, 160, 161	5139	97	1.9
Oesophagus	150	1521	82	4.9
Stomach	151	3001	20	0.7
Colon	153	13 936	146	1.0
Rectum	154	5533	189	3.4
Pancreas	157	3567	–	–
Lung	162	20 741	410	2.0
Soft tissue sarcoma	171	858	–	–
Melanoma	172	8646	–	–
Breast	174	31 133	446	1.4
Uterus	179–182	4611	–	–
Cervix	180	1825	219	12
Ovary	183	3032	269	8.9
Prostate	185	23 242	–	–
Testis	186	989	373	37.7
Bladder	188	6667	–	–
Kidney	189	3722	–	–
Brain	191	1824	68	3.7
Unknown primary site	195–199	6200	–	–
Non-Hodgkin's lymphoma	200 + 202	6217	653	10.5
Hodgkin's disease	201	846	341	40.3
Multiple myeloma	203	1721	–	–
Total		154 971	3306	2.1%

*Numbers from Ref. [22].
†Absolute numbers (see text).
‡% for individual malignancy.

gastric carcinoma. A further meta-analysis in 2000 [37], restricted to published RCTs only, showed a small survival benefit for adjuvant chemotherapy, but only in patients who had a curative resection.

A recent RCT has shown improvement in survival with chemotherapy and radiotherapy after radical surgery for adenocarcinoma of stomach and gastro-oesophageal junction [38]. At 3.3 years median follow-up, the 3-year overall survival was 52% for combined treatment vs 41% for surgery only. A node-negative D2 surgical resection was required in this RCT for improvement with adjuvant treatment [39].

An American College of Surgeons Patient Care Study for patients treated between 1982 and 1987 found that node-negative D2 surgery was only possible in 31% of people with operable stomach cancer [40]. At presentation, 20% have metastatic disease and 40% of the remainder are locally advanced or inoperable. Chemotherapy, therefore, has a curative role in the 31% out of the 40% who may be candidates for radical surgery (12% of total).

Number benefiting from chemotherapy

Australia: 1904 (incidence) × 40% (operable) × 31% (margin negative) × 11% (overall benefit) × 50% (benefit for chemotherapy) = 13 people (0.7%); SEER: 3001 × 40% × 31% × 11% × 50% = 20 people (0.7%). This is likely to be an overestimate, as data were only available for 3-year follow-up.

Colon Cancer

ICD-9: 153; incidence: 7243 (Australia), 13 936 (SEER).

Surgery is the only established curative treatment for colon cancer, with chemotherapy used as adjuvant treatment. The IMPACT Group analysis in 1995 of three separate trials of 5-fluorouracil and leucovorin in Duke's B and C colon cancer showed an improvement in 3-year disease-free survival of 9% and overall survival benefit of 5% [41]. A further meta-analysis in 1997 compared a no-treatment control with postoperative chemotherapy (excluding liver infusion) in resected colorectal cancer [16]. The overall survival benefit for chemotherapy was 5% for colon cancer and 9% for rectal cancer.

For Duke's B colon cancer, the pooled data of the IMPACT B2 group showed no improvement with adjuvant chemotherapy compared with a no-treatment control [42]. The NSABP pooled analysis of RCTs (C-01, C-02, C-03 and C-04) suggested that people with Duke's B colon cancer benefit from chemotherapy [43]. The analysis

technique has been roundly criticised, and the NSABP conclusions are therefore questionable [44,45].

A meta-analysis of portal-vein chemotherapy in colorectal cancer concluded that a survival advantage of a few percent at 5 years may occur, but an RCT involving several thousand patients would be needed to confirm this [46]. As a benefit for chemotherapy in Duke's B carcinoma has not been established, the benefit from chemotherapy is only in Duke's C colon cancers. This was 35% of the total in Australia and 21% of the total in the USA (SEER).

Number benefiting from chemotherapy

Australia: 7243 (incidence) × 35% (subgroup) × 5% (benefit from chemotherapy) = 128 people (1.8%); SEER: 13 936 × 21% × 5% = 146 people (1.0%).

Rectal Cancer

ICD-9: 154; incidence: 4036 (Australia), 5533 (SEER).

Surgery is the mainstay of treatment, with chemotherapy and radiotherapy used as adjuvant treatments. Two RCTs show that the combination of radiotherapy and chemotherapy decreased local recurrence and increased overall survival compared with a no-treatment control [47,48]. The NSABP R-02 trial [49] showed that chemotherapy alone improved disease-free survival and overall survival, and that radiotherapy alone decreased local recurrence, but had no effect on disease-free survival or overall survival. The improvement in overall survival with chemotherapy alone was 9%, although this was restricted to men. The benefit was in Duke's B and C rectal cancer. This was 60% of the total in Australia and 38% of the total in the USA (SEER).

Number benefiting from chemotherapy

Australia: 4036 (incidence) × 60% (subgroup) × 9% (benefit from chemotherapy) = 218 persons (5.4%); SEER: 5533 × 38% × 9% = 189 persons (3.4%). This may be an overestimate, as the benefit in men (48.7%) was questioned in one study and, like colon cancer, the benefit may only exist for Duke's C cancer.

Anal Cancer

Incidence: about 1% of colorectal cancers; 110 (Australia), 195 (SEER).

The combination of radiotherapy and chemotherapy for sphincter preservation is now standard management, except in advanced disease, in which abdomino-perineal resection is still required after radiotherapy and chemotherapy. In two RCTs [50,51], the addition of chemotherapy to radiotherapy gave a higher complete response rate and colostomy-free survival than radiotherapy alone, but there was no effect on overall survival.

Pancreatic Cancer

ICD-9: 157; incidence: 1728 (Australia), 3567 (SEER).

Pancreatic cancer has a 5-year survival of just over 5% [30]. The impact of gemcitabine is still being evaluated, but a recent RCT showed a median survival of 5.4 months, and a progression-free survival of 2.2 months with gemcitabine alone. An objective response was seen in only 5.6% of patients, and overall survival at 24 months was about 5% [52]. No 5-year data were available.

Lung Cancer

ICD-9: 162; incidence: 7792 (Australia), 20 741 (SEER).

Small-cell lung cancer

Incidence: 19% of total (Australia) and 13% of total in the USA (SEER).

Virtually all patients receive initial cytotoxic chemotherapy. The overall 5-year survival for small-cell lung cancer (SCLC) is 3.5%, or 2.5% in limited-stage disease and 1.2% in extensive-stage disease [53].

Non-small cell lung cancer

In early stage disease, either radical surgery or radical radiotherapy can result in long-term cure. Stage I–IIIA = 21% (Australia); 35% (SEER). A meta-analysis [54] and later a Cochrane review [55] showed that chemotherapy in addition to surgery improves overall survival by 5% at 5 years. Chemotherapy improves survival by 4% at 2 years when given in addition to radiotherapy, and was responsible for a 10% improvement in survival at 1 year compared with best supportive care. A meta-analysis of chemotherapy and radiotherapy compared with radiotherapy alone concluded that chemotherapy provides a mean gain in life expectancy of about 2 months [56]. A further analysis of RCTs of chemotherapy for non-small cell lung cancer has shown an increase in median survival of 2 months over the past 2 decades [13].

Number benefiting from chemotherapy

Australia: SCLC: 7792 (incidence) × 19% (SCLC subgroup) × 3.5% (benefit from CT) = 52 people. NSCLC: 7792 (incidence) × 81% (NSCLC subgroup) × 21% (operable) × 5% (benefit from chemotherapy) = 66 people. Total = 52 + 66 = 118 people [1.5%]; SEER: SCLC: 20 741 × 13% × 3.5% = 94 persons. NSCLC: 20 741 × 87% × 35% × 5% = 316. Total = 410 people (2.0%).

Soft Tissue Sarcoma

ICD-9: 171; incidence: 665 (Australia), 858 (SEER).

Standard care is radical surgery, radiotherapy, or both. Meta-analyses of adjuvant chemotherapy after surgery alone or after postoperative radiotherapy have shown an improvement in time to local and distant recurrence and disease-free survival, but no impact on overall survival

[57,58]. The latest Cochrane review [59] concluded that doxorubicin-based adjuvant chemotherapy seems to improve time to local and distant recurrence. There was a trend towards improved overall survival, but this was not statistically significant.

Malignant Melanoma

ICD-9: 172; incidence: 7811 (Australia), 8646 (SEER).

There is no evidence that cytotoxic chemotherapy improves 5-year survival.

Breast Cancer

ICD-9: 174; incidence: 10 661 (Australia), 31 133 (SEER).

The results of adjuvant chemotherapy have been published in several overview publications. In summary, chemotherapy reduces the rate of recurrence and improves survival for women with early breast cancer [15]. No RCTs have reported results of adjuvant chemotherapy in women aged 70 years or over, and any benefit in this age group is therefore not evidence based.

The absolute survival benefit at 5 years for chemotherapy in women less than 50 years is 6.8% for node-positive and 3% for node-negative women. For women aged between 50 and 69 years, the absolute survival benefit at 5 years is 2.1% for node-positive and 3.9% for node-negative women. A more recent RCT [60] has shown that a benefit from adjuvant chemotherapy in node-negative women aged 50–69 years is limited to women with receptor-negative disease; only 30% of node-negative women are in this group.

An analysis of surgical management of invasive breast cancer in Australia in 1995 [24] showed that 85% of women presented with early disease and 15% with advanced disease. Overall, 64% of women were node negative. Of the 10 661 women with a new diagnosis of breast cancer in Australia in 1998, 2696 women were less than 50 years and 4998 women were between 50 and 70 years. SEER data for 1998 [22] show that for women less than 50 years, 4748 were node negative and 2706 node positive. For women aged 50–70 years, 9389 were node negative and 4199 were node positive.

Number benefiting from chemotherapy

Australia: less than 50 years; node negative: 2696 (incidence) × 85% (operable) × 64% (node-negative subgroup) × 3% (benefit from chemotherapy) = 44 women. Node positive: 2696 (incidence) × 85% (operable) × 36% (node-positive subgroup) × 6.8% (benefit from CT) = 56 women. Aged 50 to 69 years: node negative: 4998 (incidence) × 85% (operable) × 64% (node negative) × 30% (ER negative) × 3.9% (benefit from chemotherapy) = 32 women. Node positive: 4998 (incidence) × 85% (operable) × 36% (node positive) × 2.1% (benefit from chemotherapy) = 32 women. Total = 164 (1.5%); SEER: less than 50 years: node negative: 4784 × 85% × 3% = 122 women; node positive: 2706 × 85% × 6.8% = 156 women. Aged 50–69 years: node negative: 9389 × 85% × 30% × 3.9% = 93 women. Node positive: 4199 × 85% × 2.1% = 75 women. Total = 446 (1.4%).

Uterine Cancer

ICD-9: 179 + 182; incidence: 1399 (Australia), 4611 (SEER).

There is no evidence that cytotoxic chemotherapy improves 5-year survival.

Cervix Cancer

ICD-9: 180; incidence: 867 (Australia), 1825 (SEER).

A meta-analysis [61], later a Cochrane Review [62], has confirmed a 12% absolute overall survival benefit with concurrent radiotherapy and chemotherapy compared with surgery alone or radiotherapy alone. There was statistical heterogeneity for outcomes, with a greater benefit for trials with a high proportion of stage I and II women.

Number benefiting from chemotherapy

Australia: 867 (incidence) × 12% (benefit from chemotherapy) = 104 women (12%); SEER: 1825 × 12% = 219 women (12%).

Ovarian Cancer

ICD-9: 183; incidence: 1207 (Australia), 3032 (SEER).

Several meta-analyses have been published [63–67]. The latest Cochrane review [68] concludes that 'the available evidence, although not conclusive, suggests that platinum-based chemotherapy is better than non-platinum therapy; that combination therapy improves survival compared with platinum alone; and no difference in effect has been shown between cisplatin and carboplatin'.

The ICON2 trial [69] reported no improvement in survival with cyclophosphamide, doxorubicin and cisplatin compared with single-agent carboplatin. The trial was stopped early due to the better response rates with the new drug paclitaxel and the ICON3 trial was undertaken. This has shown no difference between the test arm of paclitaxel and carboplatin and either of the two control arms: carboplatin alone or cyclophosphamide, doxorubicin and cisplatin [12].

Although response rates may have increased, there is no evidence that chemotherapy has improved overall 5-year survival since 1980 when platinum was standard treatment. Any improvement in overall survival in 2004 is therefore likely to be due to improvements in surgery, multidisciplinary clinics, or both.

An RCT published in the early 1980s showed that cisplatin, chlorambucil, or a combination of both, produced a 5-year survival benefit of 11% in women with advanced ovarian cancer [70]. The FIGO II–IV subgroup comprises 79% of the total (Australia) or 74% of the total (SEER).

Number benefiting from chemotherapy

Australia: 1207 (incidence) × 79% (subgroup) × 11% (benefit from chemotherapy) = 105 women (8.7%); SEER: 3302 × 74% × 11% = 269 women (8.9%).

Prostate Cancer

ICD-9: 185; incidence: 9869 (Australia), 23 242 (SEER).

There was no evidence that cytotoxic chemotherapy improves 5-year survival.

Testis Cancer

ICD-9: 186; incidence: 529 (Australia), 989 (SEER).

Seminoma of testis

Incidence: 529 × 50% of total = 265 (Australia); 989 × 59% of total = 584 (SEER).

A review article [71] concluded that chemotherapy only has a role in bulky disease with para-aortic masses over 5 cm diameter or in those who relapse after definitive radiotherapy. These patients are in the minority of those with seminoma of testis — maximum 20%.

Non-seminomatous testicular cancer

Incidence: 529 × 50% of total = 265 (Australia); 989 × 41% of total = 405 (SEER).

The outcome was changed dramatically by the use of cisplatinum [4]. The introduction of effective chemotherapy was not due to an RCT, but the results were a major improvement on previous treatment. Nowadays, up to 95% are long-term disease-free survivors, although this is less in those presenting with poor prognostic grouping. In stage I non-seminomatous testicular cancer (NSTC) (40% total), a 'surveillance' policy is standard practice, and only the 20% of this group who relapse will receive chemotherapy.

Number benefiting from chemotherapy

Australia: seminoma: 265 (incidence) × 20% (relapse) × 95% (benefit from chemotherapy) = 50; NSTC: stage I = 265 (incidence) × 40% (subgroup) × 20% (relapse) × 95% (benefit from chemotherapy) = 20; stage II–IV = 265 (incidence) × 60% (subgroup) × 95% (benefit from chemotherapy) = 151; total = 221 (41.8%). SEER: seminoma: 584 × 20% × 95% = 111; NSTC: stage I = 405 × 40% × 20% × 95% = 31; stage II–IV = 405 × 60% × 95% = 231; total = 373 (37.7%).

Bladder Cancer

ICD-9: 188; incidence: 2802 (Australia), 6667 (SEER).

Meta-analyses of neoadjuvant chemotherapy in locally advanced bladder cancer have been published [72,73]. The first, in 1995, stated that insufficient information was available and that chemotherapy could not be recommended for routine use. The second, in 2000, came to the same conclusion, but commented that, although an additional four RCTs had been completed, none had been published in full. The MRC-EORTC randomised trial [74] showed a non-significant survival benefit for chemotherapy of 5.5%, and an increase in median survival at 3 years of 8.5 months. No data were available for 5-year survival. A further RCT has shown a benefit for neoadjuvant chemotherapy and cystectomy compared with cystectomy alone [75]. A further meta-analysis showed a 5% absolute benefit at 5 years, but this was not statistically significant [76].

Number benefiting from chemotherapy

Although there may be a trend towards improved overall survival, this has not been shown to be statistically significant.

Kidney Cancer

ICD-9: 189l; incidence: 2176 (Australia), 3722 (SEER).

There was no evidence that cytotoxic chemotherapy improves 5-year survival.

Brain Cancer

ICD-9: 191; incidence: 1116 (Australia), 1824 (SEER).

A meta-analysis in 1993 suggested that chemotherapy was 'advantageous' and should be standard practice [77]. The conclusions were criticised because several published trials had been omitted and the dose of radiotherapy was suboptimal in several trials, having been reduced to allow for chemotherapy to be given [78]. A later meta-analysis of the use of multidrug or single-agent chemotherapy showed a 22% decrease in 1-year survival for multi-agent chemotherapy compared with single agent [79]. A recent Cochrane review [80] showed an absolute survival benefit of 6% for chemotherapy at 1 year, but gave no evidence of any benefit at 5 years. Analysis was confined to high-grade glioma: 82% of total (Australia); Grade II–IV 62% (USA). We have not evaluated outcome in other adult cerebral tumours.

Number benefiting from chemotherapy

Australia: 1116 (incidence) × 82% (subgroup) × 6% (benefit from chemotherapy) = 55 (4.9%); SEER: 1824 × 62% × 6% = 68 (3.7%). This is likely to be an overestimate, as only 1-year data are available.

Carcinoma of Unknown Primary Site

ICD-9: 195–199; incidence: 3161 (SEER), 6200 estimate (USA).

Most patients receive chemotherapy with essentially palliative intent [81,82]. Although 5-year survival in Australia is 13.4% for men and 11.5% for women, there is no evidence that chemotherapy is better than best supportive care plus placebo.

Hodgkin's Disease

ICD-9: 201; incidence: 341 (Australia), 846 (SEER).

Early stage disease: (I or IIA): incidence: 341 × 68% of total = 232 (Australia), 846 × 61% of total = 516 (SEER).

Radiotherapy has been the standard treatment, although there is now a move to combine chemotherapy and radiotherapy to minimise long-term complications. In a meta-analysis of the initial treatment of early stage Hodgkin's disease [83], the addition of chemotherapy to radiotherapy, or the use of more extensive radiotherapy fields, had a large effect on relapse, but only a small effect on overall survival. If initial treatment had been radiotherapy alone, many recurrences could be salvaged with chemotherapy alone or with bone-marrow transplantation. This represents an improvement in 5-year survival to 95% from 80% with radiotherapy alone.

Advanced disease (IIB–IV): incidence: 341 × 32% of total = 109 (Australia), 846 × 39% of total = 330 (SEER).

Chemotherapy is the established treatment [1]. In stage IIB–IV, Hodgkin's disease chemotherapy results in an 80% 5-year overall survival, including those receiving bone-marrow transplantation [84].

Number benefiting from chemotherapy

Australia: stage I–IIA = 232 (incidence) × 15% (benefit from chemotherapy) = 35; stage IIB–IV = 109 (incidence) × 80% (benefit from chemotherapy) = 87; total = 122 (35.8%); SEER: stage I–IIA = 516 × 15% = 77; stage IIB–IV = 330 × 80% = 264; total = 341 (40.3%).

Non-Hodgkin's Lymphoma

ICD-9: 200 + 2002; incidence: 3145 (Australia), 6217 (SEER).

Low-grade non-Hodgkin's lymphoma (NHL) is a heterogeneous group characterised by a long clinical course, with median survivals between 3 and 8 years. In stage I or II, radiotherapy often achieves long-term survival; the addition of chemotherapy does not improve survival. For stage III and IV, treatment is controversial and may involve conservative management with no treatment unless B symptoms are present or if there is disease progression. More intensive chemotherapy does not improve overall survival. With intermediate and high-grade NHL, the use of chemotherapy has improved the prognosis by inducing durable complete remission in a significant proportion of patients. However, this benefit is restricted to NHL patients with large B cell histology (30% total), where about 50% of the 70% who obtain a complete response are durable long-term survivors.

Number benefiting from chemotherapy

Australia: 3145 (incidence) × 30% (subgroup) = 944; complete response = 944 × 70% = 661; overall survival = 661 × 50% = 331 (10.5%); SEER: 6217 × 30% × 70% × 50% = 653 (10.5%).

Multiple myeloma

ICD-9: 203; incidence: 1023 (Australia), 1721 (SEER).

There is no doubt that chemotherapy and radiotherapy provide good symptom control and improve quality of life. However, a meta-analysis [85] of combination chemotherapy or melphalan plus prednisone has shown no difference in mortality, either overall or within any subgroup. There is no evidence that chemotherapy has an impact on survival.

Discussion

The 5-year relative survival rate for cancer patients diagnosed in Australia between 1992 and 1997 was 63.4% (95% CI, 63.1–63.6) [30]. In this evidence-based analysis, we have estimated that the contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults is 2.3% in Australia and 2.1% in the USA (Tables 1, 2).

These estimates of benefit should be regarded as the upper limit of effectiveness, as some eligible patients do not receive cytotoxic chemotherapy because of age, poor performance status or patient choice. Also, as noted in the text, the benefit of cytotoxic chemotherapy may have been overestimated for cancers of oesophagus, stomach, rectum and brain.

There are differences in stage distribution and cancer incidence between and within countries. However, any variation would need to be extremely large to have a major effect on the estimated percentage likely to benefit. This is demonstrated by the small effect on the survival benefit of the different proportions of Duke's C colon cancer reported in Australia and the USA (35% and 21%, respectively).

The similarity of the figures for Australia and the USA strongly suggest that a benefit of less than 2.5% is likely to be applicable in other developed countries.

For outcome data, we relied on a systematic review or a meta-analysis of RCTs of treatment outcomes rather than an individual RCT. This methodology was used to reduce the bias inherent in only presenting the results from a single positive RCT, while ignoring data from a number of negative RCTs on the same subject. Likewise we did not accept the views published by 'expert groups'. As an example, the promotion by NICE of taxanes for ovarian cancer [86] was not substantiated by ICON3 [12] or supported by another Health Technology Assessment group [87], and was later reversed [88].

Overall, only 13 out of the 22 malignancies evaluated showed any improvement in 5-year survival, and the improvement was greater than 10% in only three of those 13 malignancies. The five most 'chemo-sensitive' cancers, namely testis, Hodgkin's disease and non-Hodgkin's lymphoma, cervix and ovary, accounted for 8.4% of the total incidence in Australia in 1998. In this group, the 5-year survival rate due solely to cytotoxic chemotherapy was 14%.

The five most common adult malignancies (colorectal, breast, prostate, melanoma and lung cancer) accounted for 56.6% of the total incidence in Australia in 1998. In this

group, the 5-year survival rate due solely to cytotoxic chemotherapy was 1.6%.

The minimal impact on survival in the more common cancers conflicts with the perceptions of many patients who feel they are receiving a treatment that will significantly enhance their chances of cure. In part, this reflects the presentation of results as a 'reduction in risk' rather than as an absolute survival benefit [89,90] and by exaggerating the response rates by including 'stable disease'.

The best example of the 'over-selling' of chemotherapy is in breast cancer, where chemotherapy was introduced as the example of the new cure for solid malignancies. In Australia, in 1998, only 4638 of the 10 661 women with newly diagnosed breast cancer were eligible for adjuvant chemotherapy (44% of total). From our calculations, only 164 women (3.5%) actually had a survival benefit from adjuvant chemotherapy. In other words, on average, 29 women had to be treated for one additional woman to survive more than 5 years.

Notwithstanding, several studies have justified adjuvant chemotherapy in early breast cancer by showing that women are willing to undertake treatment for a very small benefit [91].

This does not apply to all malignancies. In lung cancer, an analysis of how patients value the trade-off between the survival benefit of chemotherapy and its toxicities showed that the willingness to accept chemotherapy as a treatment varied widely [92]. Some patients would have chemotherapy for a likely survival benefit of 1 week, and others would not choose chemotherapy for a benefit of 24 months. Others would not choose chemotherapy for any survival benefit, but would do so for an improvement in quality of life. The paper also found that some patients would not have chosen chemotherapy if they had been more fully informed.

Despite new and improved drugs, combinations and additional agents to allow for dose escalation and to prevent drug-induced emesis and neutropenic sepsis, there has been little change in the regimens used to treat 'chemo-sensitive' cancers. Examples are non-Hodgkin's lymphoma [11] and ovarian cancer [12], where CHOP and platinum, respectively, both introduced over 20 years ago, are still the 'gold standard'.

Other innovations, such as bone-marrow transplantation for breast cancer, have shown no benefit [93,94]. Similarly, the addition of anthracyclines and taxanes to adjuvant treatment of breast cancer is only likely to improve survival in the subgroups treated by an estimated 1%, but at the risk of cardiac toxicity [95] and neurotoxicity [86]. Also, recent studies have documented impaired cognitive function in women receiving adjuvant treatment for breast cancer [96], and the suggestion raised in 1977 [97] that adjuvant chemotherapy was merely a toxic means of achieving an oophorectomy is still unresolved [98].

Our analysis does not address the effectiveness or survival contribution of cytotoxic chemotherapy in the palliative or non-curative treatment of malignant disease, but the value of palliative chemotherapy has been questioned [99,100].

In breast cancer, the optimal regimen(s) for cytotoxic chemotherapy in recurrent/metastatic disease are still not defined, despite over 30 years of 'research' and a plethora of RCTs since the original Cooper regimen was published in 1969 [101]. There is also no convincing evidence that using regimens with newer and more expensive drugs are any more beneficial than the regimens used in the 1970s [102].

In addition, two systematic reviews of chemotherapy in recurrent or metastatic breast cancer have not been able to show any survival benefit [103,104]. The absence of quality-of-life data in many RCTs of cytotoxic chemotherapy has also been noted [105].

Although guidelines may exist for some uses of palliative cytotoxic chemotherapy, clinicians are not restricted from giving second, third or fourth line palliative chemotherapy in the face of progressive disease and minimal response rates. Although response rates below 15% may be due solely to a placebo effect [106,107], this fact has not been openly addressed. Indeed the whole question of the validity of response rates is very much open to debate [108,109].

This, of course, leads to a discussion of the cost implications of cytotoxic chemotherapy. Although this is a separate issue, we note that the cost of cytotoxic drugs provided by the Pharmaceutical Benefits Scheme in Australia increased from $67M for the year ended 30 June 2000 to $101.3M for the year ended 30 June 2001 [110]. The 51% increase in total drug cost was due to a 17% increase in the number of prescriptions and a 29% increase in average prescription price.

In view of the minimal impact of cytotoxic chemotherapy on 5-year survival, and the lack of any major progress over the last 20 years, it follows that the main role of cytotoxic chemotherapy is in palliation. Although for many malignancies, symptom control may occur with cytotoxic chemotherapy, this is rarely reported and, for most patients, the survival in those who obtain a response is rarely beyond 12 months.

The introduction of cytotoxic chemotherapy for solid tumours and the establishment of the sub-speciality of medical oncology have been accepted as an advance in cancer management. However, despite the early claims of chemotherapy as the panacea for curing all cancers, the impact of cytotoxic chemotherapy is limited to small subgroups of patients and mostly occurs in the less common malignancies.

Even so, any new chemotherapy drug is still promoted as a major breakthrough in the fight against cancer, only to be later rejected without the fanfare that accompanied its arrival.

In an environment of scarce resources and cost-containment, there is a need for evidence-based assessment before any new or previously accepted treatment is accepted as standard practice. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required.

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110 Pharmaceutical Benefits Pricing Authority Annual Report for the year ending 30 June 2001. Table 6a Significant Drug Groups — 12 months to end June, sorted by highest Government cost 2000–2001: pp 36, 37. http://health.gov.au/pbs/pricing/pbparpt.htm.