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Review

Levels of absolute survival benefit for systemic therapies of advanced cancer: a call for standards

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Abstract

Research on systemic interventions in patients with advanced stage malignancies should be systematised with an emphasis on the absolute gain in survival for the median patient. Such information is most meaningful with relatively large-scale evidence. Here, we summarise the survival impact of 36 interventions compared against other interventions or no treatment for advanced stage malignancies in meta-analyses of individual patient data or in selected recent (2000–2002) randomised trials with >300 randomised subjects. Although 16 interventions showed a formally statistically significant survival benefit against the comparator arm, this exceeded 3 months in only 7 cases. We propose a standardised categorisation of the median survival prolongation in trials and meta-analyses. Level 0: no proven survival benefit; level I: 0–3 months; level II: >3–6 months; level III: >6–24 months; and level IV: more than 24 months. These standardised levels may be incorporated into clinical practice guidelines for individual care and policy-making.

Keywords: Survival; Advanced stage; Cancer; Meta-analysis; Randomised controlled trials; Guidelines; Chemotherapy

1. Introduction

Over the last three decades, there has been an intense effort to identify systemic treatments that improve the outcomes of patients with advanced-stage neoplasia. The effort has translated into hundreds and thousands of randomised trials comparing diverse chemotherapeutic regimens against placebo or no treatment, against one another or against other modalities (such as immunotherapy), alone or in various combinations. For example, in an ongoing effort to identify randomised controlled trials of chemotherapeutic regimens for advanced, inoperable non-small cell lung cancer, we have already retrieved over 300 trial reports, strictly including only reports comparing different chemotherapeutic regimens. The motives for this intense clinical research effort are manifold. Cancer remains a major killer [1], advanced cancer is still a common problem despite preventive efforts, and effective treatments are thus expected to make a huge impact. Financial incentives on the part of the pharmaceutical industry may also be important to consider [2]: advanced cancer healthcare comprises a large, and unfortunately steady, market.

The net gains of this clinical research have been questioned. Several investigators have raised concerns about the overall efficacy of the tested treatments [1] advocating a shift towards prevention-oriented research. However, several plausible preventive interventions have failed miserably in their first attempts of validation in randomised trials [3,4]. Other investigators have insisted that newer modalities need to move from the bench towards clinical experimentation. However, the process is not straightforward, and unpleasant surprises such as those that occurred with gene therapy are tempering enthusiasm. For good or bad, many trials will continue to be performed on various systemic treatments among advanced cancer patients.

However, there is an imperative to understand better the magnitude of the incremental effects that each proposed regimen can achieve. Traditional approaches to interpreting therapeutic efficacy stress the importance of

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hazard ratios or odds reduction and provide absolute differences in percent survival at various durations of follow-up. Small survival differences are often supported by nice-looking P values lending credibility to plausible survival benefits. However, it is important to translate the results of clinical research into average absolute survival benefits. A simple estimate would be: how much longer would the median person with this cancer live if he/she were to receive the new treatment X rather than the older treatment Y or no treatment at all?

A quick answer can be gleaned from the Kaplan–Meier plots of any individual randomised trial with sufficient follow-up, if half the patients have been followed until death in all of the compared arms. Nevertheless, single trials may have considerable variability in their estimates due to random error, unless they are sufficiently large. Large trials and carefully conducted meta-analyses are likely to come closer to a more accurate estimate of the true average difference [5,6].

2. Methods

Table 1 shows examples from 36 interventions that have been comparatively tested against other interventions or no treatment for advanced stage malignancies in (I) meta-analyses of individual patient data or (II) selected recent single randomised trials with at least 300 randomised subjects. Meta-analyses of individual patient data on systemic interventions in advanced stage neoplastic diseases (excluding adjuvant and neoadjuvant chemotherapy and immunotherapy and excluding local treatments, e.g. radiotherapy) were identified by screening PubMed and the Cochrane Library; duplicate meta-analyses were excluded. Search strategies are available upon request. Randomised controlled trials of sample size >300 with the same disease and treatment eligibility criteria were identified by screening *The Lancet* and *New England of Medicine* for the time period of January 2000–September 2002.

3. Results and discussion

The interventions are almost equally split among those that show a statistically significant benefit ($P<0.05$, $n=16$) and those that do not show any statistically significant benefit ($P>0.05$, $n=20$). However, it is obvious that judging on the basis of statistical significance alone would be misleading. Several interventions that prolong the life of the median patient by 1 month or less compared with standard control treatments (e.g. idarubicin versus daunorubicin for acute myelogenous leukaemia (AML) [7], intravenous versus bolus 5-fluorouracil for colorectal cancer [8], or any chemotherapy added to radiotherapy for high-grade glioma [9]) are highly statistically significant in meta-analyses involving over 1000 patients. Statistical significance is based largely on the sheer numbers of randomised subjects, but the absolute magnitude of the effect is really what matters for the individual patient [10]. We will not debate whether a 1-month prolongation of life is worthwhile or not. It may well be. Safety of treatment [11] and quality of life may also be important to consider. The answer would differ from case to case and decision analyses, cost-effectiveness analyses and quality of life analyses should consider many other parameters for a final judgment.

We propose a simple categorisation of the levels of absolute survival benefit, as shown in Table 2. Most cases presented in Table 1 (29 of 36) belong to level 0 (no statistically significant benefit at all) or level I (a significant absolute survival benefit for the median patient of up to 3 months). We doubt that this is the result of some selection bias in the examples we employed. Perhaps, for some interventions, more randomised evidence would make some of the non-significant differences formally statistically significant. However, for most new interventions in advanced stage cancer, the incremental survival benefits tend to be negligible or small and we need to acknowledge this. This information should form the basis for clinical decision-making and for recommendations in practice guidelines.

Evidence-based guidelines [12] rate the available evidence by considering the study designs and the amount of the available data. We believe that besides the quality of design, and the amount of data, an estimate of the absolute observed incremental benefit is important to present. The picture may be sobering for many advanced stage cancers, but we should try to be as accurate as possible to our patients and to ourselves as we delve through more, newer, complex and expensive therapeutic options. Such a categorisation communicates in a common language whether newer treatments are truly important advances, for survival at least. We can code the incremental benefits of each newer therapeutic step as new interventions appear.

The overall benefit of an intervention may reflect the net sum of the incremental benefits of each of the previously tested therapeutic advances over the history of systemic treatments employed for a specific tumour. It is misleading and plain wrong to compare the median survival of patients in the distant past with the median current survival of patients from the same tumour at the same stage and attribute triumphantly the difference to the latest available regimen. In some cases, the difference might be largely due to other, totally unrelated reasons surrounding cancer diagnosis and care, as well as evolving differences in the prognostic factor distribution of treated patients, and only minimally due to therapeutic advances. Four successive steps in the treatment of one tumour where each time the newer regimen conveyed no survival benefit over the previous

Table 1
Selected meta-analyses and randomised controlled trials for various interventions in advanced stage neoplastic disease

Year	Neoplasia	Intervention	Trials (*N*)	Median gain[a]	*P* value[a]	Level
Meta-analyses of individual patient data						
1998	AML	Idarubicin versus daunorubicin	5 (1052)	1 (10 versus 9)	0.03	I
1999	CLL	Any combination chemotherapy versus chlorambucil	9 (1926)	0 (58 versus 58)	>0.10	0
1997	CML	Alpha interferon versus chemotherapy	7 (1554)	20 (70 versus 50)	<0.001	III
2000	CML, Ph+	Hydroxyurea versus busulphan	3 (690)	7 (52 versus 45)	0.1	0
2001	Multiple myeloma	Alpha interferon	24 (4012)	4 (40 versus 36)	0.01	II
1998	Multiple myeloma	Combination chemotherapy versus melphalan + steroids	20 (4930)	0 (28 versus 28)	0.6	0
2001	Breast cancer	Tamoxifen + LHRH agonist versus LHRH agonist	4 (506)	6 (37 versus 31)	0.02	II
1992	Colorectal cancer	5-FU + leucovorin versus 5-FU	9 (1381)	1 (12 versus 11)	0.51	0
1998	Colorectal cancer	Intravenous versus bolus 5-FU	6 (1219)	1 (12 versus 11)	0.039	I
2000	Colorectal cancer	Any palliative chemotherapy	13 (1365)	4 (12 versus 8)	<0.001	II
1994	Colorectal cancer	5-FU + methotrexate versus methotrexate	8 (1178)	2 (11 versus 9)	0.024	I
1996	Colorectal cancer	Intra-arterial hepatic infusion	7 (654)	4 (15 versus 11)	<0.001	II
2002	Glioma, high-grade	Any chemotherapy	12 (3004)	1 (11 versus 10)	<0.001	I
1995	Non-small cell lung cancer	Cisplatin chemotherapy	8 (778)	2 (6 versus 4)	<0.001	I
1995	Non-small cell lung cancer	Chemotherapy + radiotherapy versus radiotherapy	22 (3033)	2 (13 versus 11)	0.006	I
1991	Ovarian cancer	Combination versus single non-platinum chemotherapy	16 (3146)	0 (13 versus 13)	0.42	0
1991	Ovarian cancer	Platinum combination versus single non-platinum	11 (1136)	2 (17 versus 15)	0.3	0
1998	Ovarian cancer	Platinum versus no platinum	9 (1704)	3 (19 versus 16)	0.02	I
1998	Ovarian cancer	Platinum combination versus single agent platinum	9 (1095)	2 (22 versus 20)	0.21	0
1998	Ovarian cancer	Cisplatin versus carboplatin	12 (2219)	0 (24 versus 24)	0.66	0
2000	Prostate cancer	Maximum androgen blockage	27 (8275)	1 (28 versus 27)	0.11	0
Randomised controlled trials						
2000	CLL	Fludarabine versus chlorambucil	1 (509)[b]	10 (66 versus 56)	>0.10	0
		Fludarabine + chlorambucil versus chlorambucil		0 (55 versus 56)	>0.10	0
2002	Lymphoma, DLBC	Rituximab + CHOP versus CHOP	1 (399)	NE[c] (>36 versus 21)	0.007	III/IV
2000	Breast cancer	High-dose chemotherapy + stem cell versus chemotherapy	1 (553)	0 (24 versus 26)	0.23	0
2001	Breast cancer	Trastuzumab + chemotherapy versus chemotherapy	1 (469)	5 (25 versus 20)	0.046	II
2000	Colorectal cancer	Irinotecan + 5-FU + leucovorin versus 5-FU + leucovorin	1 (683)[b]	2 (15 versus 13)	0.04	I
		Irinotecan versus 5-FU + leucovorin		0 (12 versus 13)	>0.10	0
2000	Colorectal cancer	Irinotecan + 5-FU versus 5-FU	1 (387)	3 (17 versus 14)	0.031	I
2002	Colorectal cancer	Lokich regimen versus de Gramont regimen	1 (905)[b]	0 (10 versus 10)	0.17	0
		Raltitrexed versus de Gramont regimen		0 (9 versus 10)	0.94	0
2001	Non-small cell lung cancer	Docetaxel + cisplatin versus gemcitabine + docetaxel	1 (441)	0 (10 versus 10)	0.58	0
2002	Non-small cell lung cancer	Cisplatin + gemcitabine versus cisplatin + paclitaxel	1 (1207)[b]	0 (8 versus 8)	>0.10	0
		Cisplatin + docetaxel versus cisplatin + paclitaxel		0 (7 versus 8)	>0.10	0
		Carboplatin + docetaxel versus cisplatin + paclitaxel		0 (8 versus 8)	>0.10	0
2002	Ovarian cancer[d]	Paclitaxel + carboplatin versus standard chemotherapy	1 (2074)	1 (36 versus 35)	0.74	0

AML: acute myelogenous leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; Ph+, Philadelphia chromosome-positive; LHRH, luteinising hormone-releasing hormone; 5-FU: 5-fluorouracil; DLBC, diffuse large B-cell; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone.

[a] The median gain is the difference (in months) of median survival derived from presented Kaplan–Meier plots (set as 0 when the experimental arm performs worse than the control arm), the *P* value is based on the original analysis of the data in the meta-analysis or randomised controlled trial.

[b] Sum of patients in all of the compared arms.

[c] Not estimable, since patients were not followed enough for median survival estimates (data pertain to survival of the 40th patient)

one, will not translate to an overall 12 or 24 months gain in survival due to the most recent therapy compared with no therapy. Conversely, four steps with level I survival benefit each may translate to an overall level II, or occasionally level III benefit for the newest regimen compared with the no treatment option. Some cancers, such as breast cancer or colorectal cancer, may have such a history of added incremental benefits. Nevertheless, we still need to be cautious in claiming large improvements. For most tumours, trials testing the most recent, 'state-of-the-art' treatment against no

Table 2
Levels of median survival prolongation

Level	Survival
Level 0	No proven survival prolongation
Level I	Up to 3 months survival prolongation
Level II	>3–6 months survival prolongation
Level III	>6–24 months survival prolongation
Level IV	Over 24 months survival prolongation

treatment may never be performed as they would be considered unethical. Conversely, the uncertainty about the median gain for each incremental step can be substantial and it adds up multiplicatively when several incremental steps are considered. Thus, we need to tone down on easy claims for major therapeutic advances, and simply and quietly scrutinise the evidence one step at a time.

Although we used meta-analyses of individual patient data and randomised trials to illustrate the proposed survival levels, this approach can be used with any kind of research evidence. However, with smaller sizes, the uncertainty about the level of incremental survival benefit may be too large. Often, even with several hundreds of patients, uncertainty may amount to at least one level of survival benefit, occasionally even more.

This categorisation may also be expanded to the appraisal of efficacy of therapeutic interventions in earlier stage disease. For earlier stages, it may be preferable to use the survival difference for the 40th or even 25th percentile patient, since in most cases it is unlikely that we will ever get enough follow-up to present the median survival for patients with early-stage disease. The same may be true for a few selected advanced stage malignancies where the prognosis is already very good and cure is a real probability, e.g. Hodgkin's disease [13] and germ cell tumours [14]. Regardless of the disease stage, an estimate of how much time a patient has to gain from selecting a specific treatment course over another would be useful to acknowledge, both for individual decision-making and for policy-making.

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