Trends in the Use and Role of Biomarkers in Phase I Oncology Trials

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Abstract

Purpose: There has been interest in using biomarkers that aid the evaluation of new anticancer agents. We evaluated trends in the use of biomarkers and their contribution to the main goals of phase I trials.

Experimental Design: We did a systematic review of abstracts submitted to the American Society of Clinical Oncology annual meeting from 1991 to 2002 and the publications related to these abstracts. We analyzed the use of biomarkers and their contribution to published phase I trials.

Results: Twenty percent of American Society of Clinical Oncology phase I abstracts (503 of 2458) from 1991 to 2002 included biomarkers. This proportion increased over time (14% in 1991 compared with 26% in 2002; $P < 0.02$). Independent predictors of the use of biomarkers included National Cancer Institute sponsorship, submission in the time period of 1999 to 2002, adult population, and drug family (biological agents). Biomarkers supported dose selection for phase II studies in 11 of 87 of the trials (13%) emanating from these abstracts. However, the primary determinants of phase II dose and schedule were toxicity and/or efficacy in all but one of these 87 trials (1%). Biomarker studies provided evidence supporting the proposed mechanism of action in 34 of 87 of the published trials (39%).

Conclusions: The use of biomarkers in phase I trials has increased over the period from 1991 to 2002. To date, biomarker utilization has made a limited and primarily supportive contribution to dose selection, the primary end point of phase I studies. Additional studies are needed to determine what type of biomarker information is most valuable to evaluate in phase I trials.

Biomarkers have been suggested to be potentially useful end points for phase I trials of new anticancer agents (1). Several factors explain the growing interest for cancer biomarkers. First, the advent of molecularly targeted drugs entering clinical trials has stimulated the use of biomarkers to correlate clinical empirical data with target modulation. Second, advances in biotechnology have allowed the creation of accessible test modalities that measure specific tumor targets, such as special imaging studies (e.g., fluorodeoxyglucose–positron emission tomography, dynamic magnetic resonance imaging) and immunohistochemistry studies, such as receptor expression and protein phosphorylation patterns (2–5). Third, the failure of many cytostatic, molecularly targeted drugs to show substantial rates of objective clinical response has motivated drug sponsors to seek molecular and biochemical evidence of target engagement during early stages of drug development (6).

The actual importance of novel biomarkers as end points in phase I trials has not been carefully studied. Biomarkers may help define the biologically active dose and schedule for phase II studies and may help confirm mechanisms of action. Biomarkers may also serve as surrogate end points for drug resistance, clinical toxicity, and clinical efficacy, if clinically validated (1). Some biomarkers have also helped define subgroups of cancers more likely to respond to experimental therapies, as shown in trials of trastuzumab and hormonal therapies of breast cancer and in trials of imatinib mesylate (in gastrointestinal stromal tumors; refs. 7–9). Despite the successful use of biomarkers in the development of these drugs, a comprehensive analysis of the role of biomarkers in phase I trials could be informative in assessing their general value in phase I trials.

Therefore, we conducted an analysis of trends in the use of biomarkers in phase I trials, based on a review of abstracts submitted to American Society of Clinical Oncology (ASCO) from 1991 to 2002. We evaluated the effect of biomarker measurements on dose and schedule chosen for phase II, as determined from papers published on the above abstracts, as well as whether biomarker measurements added significantly to the understanding of drug mechanism of action. Based on this review of abstracts and publications, we provide a classification of different types of biomarkers and an evaluation of their contribution to the early development of new drug candidates in phase I trials.

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Materials and Methods

Abstract analysis

Data acquisition. We developed a database of abstracts of phase I clinical trials submitted to the American Society of Clinical Oncology (ASCO) annual meeting from 1991 to 2002, as previously described (10). Briefly, we reviewed all abstracts of phase I therapeutic trials during this time period and analyzed their baseline characteristics and time trends for inclusion of biomarkers. We collected general data from abstracts because they provide a more representative sample of phase I trials done in the United States and abroad, are easily accessible, and suffer from less publication bias compared with journal articles. General data recorded included drug family; year of abstract submission; inclusion, type, and source of biomarkers; inclusion of pharmacokinetics; National Cancer Institute (NCI) sponsorship or industry sponsorship; trial location; and patient population (adult versus pediatric). To analyze the contribution of biomarkers to the end points and conclusions of phase I trials from this time period, we reviewed published articles, as they contain more detailed information about the role of biomarkers in the trials. We searched MEDLINE for published articles emanating from the ASCO abstracts using the first and last author's names and the generic name of the subject compound (Fig. 1).

Eligibility criteria: abstracts. All phase I therapeutic trials were initially eligible for analysis. We then excluded (*a*) abstracts that reported pharmacokinetics or biomarker results separately from clinical results, (*b*) trials without therapeutic intent (e.g., chemoprevention), (*c*) supportive treatment trials (e.g., colony stimulation factors), (*d*) trials with healthy volunteers, and (*e*) trials in which the source of biomarkers was not identified.

Published articles. We included only single-agent phase I trials for compounds that were not yet approved for marketing by the Food and Drug Administration at the time of abstract submission. Trials that included radiation therapy or a phase II component in their design were excluded.

Selection of biomarkers. We defined a biomarker as any biological variable, either genetic or phenotypic, that was measured by molecular, biochemical, or imaging techniques. In the case of molecular and biochemical biomarkers, we required at least one measurement before and after therapy with the studied compound. Imaging studies of immunoscintigraphy for radio-labeled antibodies were included without a pretherapy imaging study. For analysis of published trials, we required that biomarker measurement was described or referenced in detail in the Materials and Methods section of each article. Peer reviewed trials must have reported biomarker studies in at least five subjects to be considered eligible for analysis. Abstract analysis did not require a minimum number of subjects who participated in biomarker studies. We did not consider common markers of tumor response to treatment, such as reduction of tumor size on standard imaging tests (computed tomography or magnetic resonance imaging scans) or serum tumor markers (e.g., PSA, CA 19-9, CEA) as biomarkers for the purpose of our study. Common clinical end points of toxicity, such as blood counts, were not considered biomarkers for this study, nor were pharmacokinetic studies. For trials that included multiple biomarkers, we analyzed the one we considered to be the primary biomarker to simplify data acquisition and analysis. The primary biomarker for each study was defined as the one which had the greatest potential effect on the predetermined goals of the trial as identified by consensus among the four investigators responsible for data abstraction and analysis. Table 1 provides a classification of the types of biomarkers identified in our study.

Source of biomarkers. As shown in Table 1, we classified the sources of biomarkers as serum, peripheral blood mononuclear cells (PBMC), special imaging methods, normal tissue (defined by biopsies of solid organs not involved by tumors, such as skin or bone marrow), tumor tissue (including malignant effusions), and cerebrospinal fluid.

Baseline characteristics of phase I trials. We determined the number and proportion of trials that included biomarker studies as a function of various baseline characteristics of the trials. Baseline characteristics include period (1991-1994 versus 1995-1998 versus 1999-2002), drug family of the studied compound (cytotoxic versus biological versus molecularly targeted small molecules versus other), pharmacokinetic studies (yes versus no), NCI or industry sponsorship, trial location (United States versus other country), and patient population (adult versus pediatric). We defined cytotoxics as compounds that directly inhibit the replication of cells by acting on DNA synthesis or processing. Molecularly targeted agents were defined as molecules that inhibit cell proliferation, tumor invasion, or angiogenesis or decrease cell survival by acting on specific cellular biochemical targets other than direct inhibition of DNA synthesis or processing. Biological compounds consisted of proteins (e.g., monoclonal antibodies) or nucleic acid–based agents (e.g., antisense oligonucleotides). Drugs were assigned to the "other" category when the description of mechanism of action provided by abstracts was unclear or lacking.

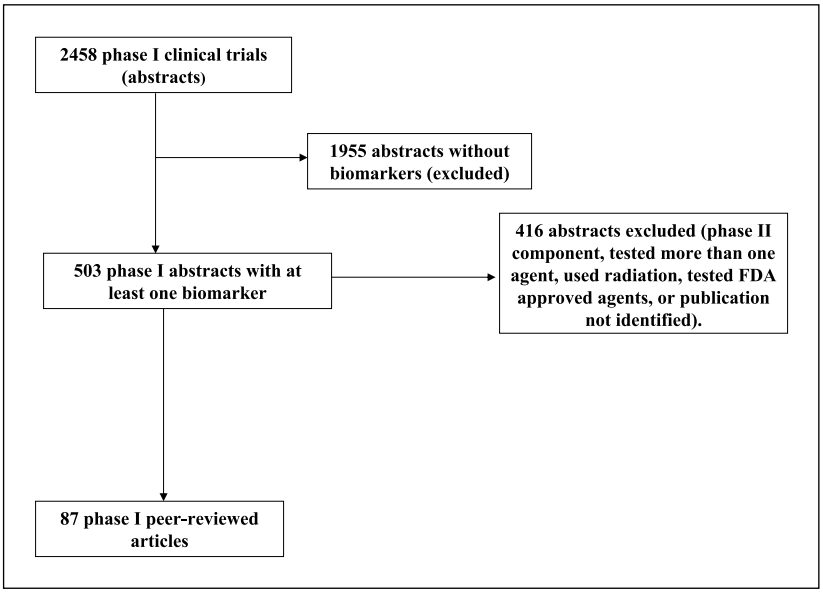

Fig. 1. Flow chart showing the selection of the 87 eligible phase I trials published in the literature and used for more detailed analysis of biomarker utilization as analyzed in Table 3.

Table 1. Description and proportions of biomarkers included in 503 ASCO phase I abstracts from 1991 to 2002

Types of biomarkers according to source	No. trials (%)
Serum	185 (36.7)
Immunologic studies*	74 (14.7)
Cytokine levels	22 (4.3)
Other protein levels	22 (4.3)
Hormone levels	10 (1.9)
Angiogenic factors †	7 (1.3)
Nucleoside levels	6 (1.1)
Not specified	12 (2.3)
Tumor tissue	129 (25.6)
Histopathologic analysis	21 (4.1)
Protein expression ‡	21 (4.1)
Gene expression ‡	18 (3.5)
Protein expression immunohistochemistry§	16 (3.1)
PCR-DNA or RNA	11 (2.1)
Receptor expression immunohistochemistry§	9 (1.7)
Enzyme activity‖	8 (1.5)
PBMC	114 (22.6)
Enzyme activity‖	27 (5.3)
DNA synthesis	19 (3.7)
Protein expression ‡	9 (1.7)
Immunologic studies*	8 (1.5)
Gene expression ‡	6 (1.1)
Not specified	9 (1.7)
Special imaging	55 (10.9)
Dynamic magnetic resonance imaging	16 (3.1)
Immunoscintigraphy	15 (2.9)
Positron emission tomography scans	10 (1.9)
Radio-labeled drugs	9 (1.7)
Normal solid tissues	19 (3.7)
Cerebral spinal fluid	1 (0.2)
Total	503 (100)

NOTE: All biomarkers used in 1% or less of the abstracts are listed in the footnote and included in the total number of biomarkers of each subcategory of biomarkers in the table. The following biomarkers were adopted in 1% or less of the abstracts. Serum: lipid levels (2 abstracts), magnetic resonance imaging spectrophotometry (2 abstracts), amino acid levels (1 abstract), neurotransmitter metabolites (1 abstract); Tumor tissue: immunohistochemistry-NOS (4 abstracts), DNA synthesis (3 abstracts), epigenetic studies – DNA methylation and histone acetylation tests (3 abstracts), flow cytometry – tumor cells (2 abstracts), immunologic studies (2 abstracts), nucleoside levels (2 abstracts), RNA expression (2 abstracts), P-glycoprotein activity (1 abstract), radio-labeled drug (1 abstract), receptor expression (1 abstract), signal transduction proteins (1 abstract), immunofluorescence-NOS (1 abstract), tumor cell proliferation study (1 abstract), not specified (1 abstract). PBMC: RNA expression (4 abstracts), tubulin polymerization (3 abstracts), protein expression – Western blot (3 abstracts), protein expression immunohistochemistry (3 abstracts), receptor expression (3 abstracts), cytokine levels (3 abstracts), flow cytometry – leukocytes (3 abstracts), signal transduction proteins (2 abstracts), epigenetic studies (2 abstracts), radio-labeled drug (1 abstract), PCR-RNA (1 abstract), receptor expression immunohistochemistry (1 abstract), gene microarray (1 abstract), intracellular glutathione levels (1 abstract), P-glycoprotein activity (1 abstract), intracellular pharmacokinetics (1 abstract), drug efflux studies – without multidrug resistance-1 or P-glycoprotein expression studies (1 abstract), kariotype studies (2 abstracts). Normal solid tissues: histologic analysis (4 abstracts), immunologic studies (3 abstracts), enzyme activity (3 abstracts), receptor expression immunohistochemistry (2 abstracts), immunohistochemistry-NOS (2 abstracts), protein expression immunohistochemistry (2 abstracts), PCR-NOS (1 abstract), flow cytometry (1 abstract), other (1 abstract). Special imaging: single-photon emission computed tomography (4 abstracts), other (1 abstract). Cerebral spinal fluid: PCR-NOS (1 abstract).

*Immunologic studies included skin biopsies for local immunization reactions, lymphoproliferative responses in blood and PBMCs, T-cell subpopulation counts (CD4, CD8), natural killer cell counts, specific antibody levels, immunoglobulin fractions (Fab, Fc), complement levels, delayed hypersensitivity test, markers of lymphocyte differentiation, human antimonoclonal antibody levels, and human antitoxin antibody levels.

†Vascular endothelial growth factors and fibroblast growth factor (b-FGF).

‡Techniques of measurement were not reported.

§Signal transduction protein studies include markers of expression and/or activity of proteins involved in cell cycle regulation pathways, such as cyclin-dependent kinases, mitogen-activated protein kinases, etc.

‖Examples of enzyme activity include receptor-tyrosine kinase activity, thymidylate synthase activity, dihydrofolate reductase activity, protein kinase C activity, etc.

Factors associated with inclusion of biomarkers in phase I trials. We used the above baseline characteristics as variables to develop a multivariate model to identify factors associated with inclusion of biomarker studies in phase I trials.

Time trends of use of biomarkers. For each year, we determined the proportion of trials as represented in ASCO abstracts that included biomarkers. We divided the number of abstracts with biomarkers by the total number of phase I abstracts for each year from 1991 to 2002.

Journal articles analysis

Contribution of biomarkers to phase I trials: published articles. After we identified eligible articles through the MEDLINE search, we analyzed

the contribution of biomarkers to the following goals of phase I trials: (*a*) dose selection for phase II studies; (*b*) schedule selection for phase II studies; (*c*) support for the proposed mechanism of action of the drug as shown, for example, by target engagement or inhibition of a pathway. Biomarkers measured as continuous variables needed to show dose dependency regarding target modulation to be considered supportive of dose. Dose dependency was defined as consistently positive or negative, but not necessary linear, relationships between the dose of the studied compound and the changes in biomarker measurement from the baseline pretherapy values. In other words, if biomarker measurements consistently increased or decreased in response to increasing doses of the studied compound, dose-dependency was considered to be present. A positive contribution for dose selection was defined as the presence of a dose-dependent relationship (either positive or negative), but not necessarily linear, between the changes in biomarker measurement and increasing doses of the studied compound. For schedule selection, biomarker contribution was defined as changes in biomarker measurements pointing toward maximum target inhibition or stimulation evident from different schedules of the studied compound when different schedules were compared within the same dose cohort of the drug. Biomarker contribution to confirmation of mechanisms of action occurred whenever biomarker changes reflected the effect of the drug on the targeted molecular pathway believed to lead to an antitumor effect. We did the analysis of contribution independently for each goal (i.e., a biomarker could make a contribution to more than one goal in the same article).

We also determined the number of trials in which biomarkers were used to select a patient population either before the beginning of the trial (i.e., as an inclusion criterion) or recommended by the authors as potentially useful for patient selection in future studies of the same agent or agent class.

Because our classification system is subject to investigator bias, two participants (H.H.P. and B.H.G.) classified the contribution of biomarkers independently. Discrepant results were resolved by discussion. These results were then further reviewed by two participants with experience in cancer biomarker utilization and phase I trials (J.W.C. and B.A.C.). Only those results considered positive in contribution by all four reviewers were recorded as positive. To quantify the contribution of biomarkers as single determinants of the dose and schedule for phase II studies, we then identified the articles in which the biomarker information was used to determine the proposed dose for additional study, independent of dose and schedule determination based on toxicity and/or clinical efficacy data.

Statistical analysis. We used the Cochran-Armittage test for linear trend to determine the time trends for the inclusion rate of biomarkers over time. We used stepwise logistic regression for the multivariate model of predictors of inclusion of biomarkers. We considered P of <0.05 as statistically significant for both analyses. We report the odds ratio of inclusion of biomarkers only for the baseline characteristics that we found to be independent predictors after the logistic regression analysis. We did not perform a formal statistical analysis of the contribution of biomarkers to phase I trials.

Results

Abstracts

Analysis of abstracts. We identified 2,458 abstracts of phase I clinical trials eligible for analysis. Of these, 20% (503 of 2458) included at least one biomarker. Our MEDLINE search identified 87 published articles based on these abstracts (Fig. 1). Fifteen articles did not meet all criteria for inclusion: seven articles were without pre- and posttherapy measurements of biomarkers, six were with fewer than five subjects participating in biomarker studies, and two were with no clear biomarker study. We describe the results for all 87 trials according to the "intent to treat" principle.

Types of biomarkers. Table 1 shows a description of the biomarkers and their frequency of use in 503 abstracts. Serum markers were the most common source of biomarkers (185 of 503, 36.7%), followed by tumor tissue (129 of 503, 25.6%), PBMC (114 of 503, 22.6%), and novel imaging studies (55 of 503, 10.9%). Biomarkers measured in normal tissues were described in 19 abstracts (3.7%) with histologic analysis, immunologic studies (skin biopsies for local immunization reactions), and enzyme activity measurements representing the most common biomarkers of this category.

Overall, biomarkers composed a highly heterogeneous group of studies. Of the 503 primary biomarkers (one for each abstract), the most common types were immunologic studies (82 of 503, 16.3%; Table 1). Measurement of enzyme expression level or activity in a normal or malignant tissue was the second most prevalent type of biomarker (35 of 503, 6.9%). Ninety-two (18.3%) different types of biomarkers were each used in <1% of the abstracts (Table 1).

Factors associated with inclusion of biomarkers. A multivariate model identified four baseline characteristics that are associated with the use of biomarkers: drug family (biological and molecularly targeted versus cytotoxic), study population (adult versus pediatric), NCI sponsorship (yes versus no), and period (1999-2002 versus 1991-1994). Of these, the strongest determinant was drug family (biological agents versus cytotoxics; odds ratio, 17.0; 95% confidence interval, 13.0-25.0). The overall concordance of the multivariate model was 87.4%. The respective odds ratio for each factor is shown in Table 2.

The proportion of trials that included biomarkers has significantly increased over the 11 years of this study, as shown in Fig. 2. In 1991, 14% of the abstracts reported the inclusion of biomarkers compared with 26% of the abstracts reported in 2002 ($P_{\text{trend}} < 0.02$). The time trend remains significantly positive even if we change the time unit from 1-year period to 4-year period (Table 2).

Journal articles

Of the 87 articles, 32 (37%) had more than one biomarker, and a consensus among the four abstractors (B.H.G., H.H.P., J.W.C., and B.A.C.) was reached to select the biomarker most likely to aid in achieving the goals of phase I trials. Of the 32 trials with more than one biomarker, 14 (44%) described two biomarkers, 10 (31%) described three biomarkers, and 8 (25%) trials had four or five biomarkers.

Contribution of biomarkers to the goals of phase I trials: published articles. To determine the effect of biomarkers on choice of drug dose and schedule, we reviewed 87 published articles emanating from the 503 abstracts that had used biomarkers in their trial design and analysis as identified above. On average, 18 subjects per trial participated in biomarker studies (range, 0-92). Fifty-two trials (60%) evaluated biological (recombinant) agents, 25 (29%) studied targeted drugs, and 10 (11%) tested cytotoxic drugs. The contribution of biomarkers to the goals of these trials is summarized in Table 3. Biomarkers contributed to dose selection for subsequent phase II studies in 11 of the 87 trials (13%; i.e., in 13% of the trials the information provided by the biomarker influenced the choice of the dose for a phase II study). In seven trials (8%), biomarkers contributed to the selection of a schedule for phase

Table 2. Multivariate analysis of factors associated with inclusion of biomarkers in 2,458 phase I abstracts from 1991 to 2002

Baseline characteristics	Trials with biomarkers/total number of trials (%)*	Odds ratio (95% CI) †
Drug family		
Cytotoxic ‡	110/1472 (7)	Reference
Biological§	213/383 (55)	17.0 (13.0-25.0)
Targeted‖	136/398 (34)	
Other	44/205 (21)	NA
Population		
Pediatric	3/71 (4)	Reference
Adult	500/2387 (21)	8.0 (2.4-27.0)
NIH sponsorship		
No	387/2132 (18)	Reference
Yes	116/326 (35)	2.8 (2.0-3.7)
Period		
1991-1994	108/650 (16)	Reference
1995-1998	143/760 (19)	NA
1999-2002	252/1048 (24)	2.2 (1.7-2.9)
Pharmacokinetics		
No	237/1289 (18)	Reference
Yes	266/1169 (22)	NA
Industry sponsorship		
No	258/1378 (19)	Reference
Yes	245/1080 (22)	NA
Trial location		
USA	377/1575 (24)	Reference
Other	124/875 (14)	NA
Not given	2/8 (25)	NA

Abbreviation: NA, not applicable.
*Total number of trials was determined for each characteristic (row).
†We report the odds ratio of significant independent predictors only ($P < 0.05$).
‡Compounds that kill tumor cells by targeting the DNA or its machinery.
§Macromolecules similar to endogenous molecules produced by recombinant technology (e.g., antibodies, cytokines, antisense oligonucleotides, etc.).
‖Small molecules that kill tumor cells or produce cell cycle arrest by affecting specific biochemical pathways.

II studies. However, the information from biomarkers was only used directly in one study (1%) to determine the dose for a subsequent study in the absence of efficacy or toxicity end points. In all of the other 86 studies, the maximum tolerated dose (MTD) and/or evidence of efficacy (response rates) were the defining factors for phase II dose and schedule selection.

In 34 of the 87 trials (39%), biomarkers provided evidence to support the proposed mechanism of action of the drug. In 11 of the 87 trials (13%), biomarkers were used to select a patient population for phase I enrollment, and in 17 trials (19%), biomarkers were considered by the authors to be potentially useful for selecting a patient population in subsequent studies.

The contribution of biomarker studies to the goals of phase I trials varied according to the source of biomarkers (Table 3). In none of the studies that used urinary biomarkers and imaging biomarkers or studies of normal tissues did these measurements play a significant role in supporting dose and schedule selection for subsequent phase II studies. In contrast, in 6 of 19 studies (32%) using tumor tissue biomarkers, the test contributed to dose for phase II studies. Eleven of 19 studies (58%) of tumor tissue biomarkers provided evidence to support the proposed mechanism of action of the agent, as did 4 of 6 studies (67%) of normal tissues, 3 of 9 imaging studies (34%), 9 of 20 PBMC studies (45%), and 7 of 32 serum biomarkers (22%). Of the 11 trials of tumor tissue biomarkers that supported the proposed mechanism of action, two studies analyzed selective antibody binding to tumor target (immunoconjugates BR96-doxorubicin and N901-blocked ricin, respectively), three studies evaluated enzyme inhibition (tyrosine kinase assays for inhibition by imatinib and antibody RG 83852 and one study of polyamine biosynthesis inhibition by SAM486A), five studies evaluated efficacy of recombinant gene transfection from plasmids, and one study measured down-regulation of HER-2 receptor after E1A gene therapy.

Discussion

The development of oncology drugs compared with drugs of other diseases has one of the highest failure rates (11). One primary reason for such high attrition rates is believed to be the lack of rigorous and predictive animal models which properly reflect human experience (11). As such, the utilization of biomarkers in phase I clinical trials is appealing due to their potential to serve, if prospectively validated, as surrogates for drug efficacy and toxicity and to evaluate effects on molecular targets. Ideally, the use of biomarkers in early trials would help predict the likelihood of success or failure of a drug in efficacy trials, guide selection of patients more likely to respond to the agent, and provide meaningful correlations with toxicity and response. The actual value of biomarkers for achieving these objectives in phase I trials has not yet been defined. The question of whether biomarkers actually help investigators to achieve the main goals of phase I trials, which include the selection of dose and schedule for phase II studies and estimates of safety and efficacy also remains unquantified. Our systematic review of articles included predominantly phase I trials of biological and targeted agents, wherein most of the interest in the development of biomarkers is concentrated.

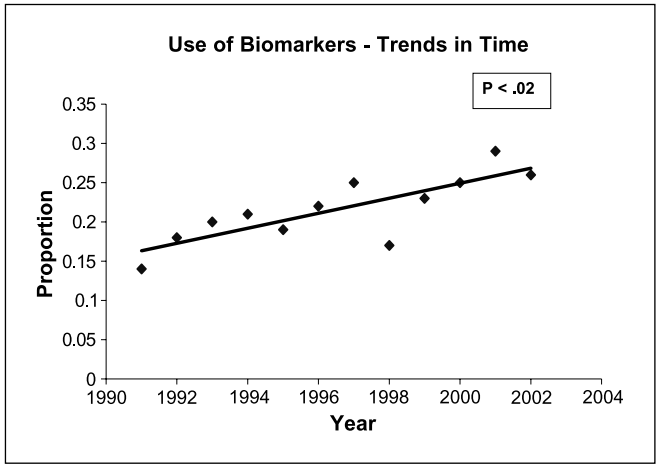

Fig. 2. Graph of the proportion of inclusion of biomarkers in phase I clinical trials from 1991 to 2002. The proportions correspond to the number of trials that adopted at least one biomarker in each year divided by the total number of phase I trials in that year. The P value was obtained by the Cochran-Armitage test for linear trend.

Table 3. Proportions of trials with biomarkers that influenced dose selection for phase II studies, schedule selection for phase II studies, showed evidence consistent with the proposed mechanism of action, and were considered for patient selection in 87 published phase I clinical trials

Source of biomarkers	Dose (%)	Dose contribution independent of MTD (%)	Schedule (%)	Mechanism of action (%)	Patient selection (%)*
Serum (n = 32)	3 (9)	0 (0)	3 (9)	7 (22)	6 (19)
PBMC (n = 20)	2 (10)	0 (0)	3 (15)	9 (45)	3 (15)
Urine (n = 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tumor tissue (n = 19) †	6 (32)	1 (5)	1 (5)	11 (58)	5 (26)
Normal tissue (n = 6) ‡	0 (0)	0 (0)	0 (0)	4 (67)	1 (17)
Imaging (n = 9)§	0 (0)	0 (0)	0 (0)	3 (34)	4 (45)
Total (n = 87)	11 (13)	1 (1)	7 (8)	34 (39)	19 (22)

NOTE: Proportions were obtained by dividing the number of trials with biomarkers that made a contribution by the total number of trials for each source.

*Biomarkers used to select patient populations at the start of the trial or considered useful for future studies at the end of the trial based on the article author's opinion.

†Included specimens from both solid and hematologic malignancies.

‡Included normal bone marrow specimens from patients with solid malignancies (3 studies), normal skin biopsies (2 studies), and normal buccal mucosa (1 study).

§Included five studies of body distribution of the compound: four radioimmunoscintigraphy and one single-photon emission computerized tomography studies, three tumor vascular perfusion studies (dynamic magnetic resonance imaging), and one [^{18}F]fluorodeoxyglucose–positron emission tomography scan.

Biomarkers only modestly contributed to the selection of dose and schedule for phase II studies, but helped support the mechanism of action of phase I agents in a significant proportion of phase I trials (39%).

We found that the number of phase I trials that included biomarkers has steadily increased over the period under study, 1991 to 2002. In addition, phase I trials of biological and targeted agents were more likely to include a new biomarker compared with trials of cytotoxic agents. This increased utilization of biomarkers for trials of biological and targeted agents is understandable, because the optimal dose for biological and molecularly targeted agents may be lower than MTD (12).

The prevalence of biomarker usage in early-phase oncology trials relative to other disease areas is difficult to assess due to the scarcity of systematic studies of early-phase biomarker utilization. Of the 274 trials in cardiology (187) and rheumatology (87) listed on the ClinicalTrials.gov Web site in March 2007, only six of the 27 nonrandomized (as a surrogate marker for early trials because very few of the trials are phase I trials) therapeutic interventional studies list biomarker evaluation as an objective. In four of these, the biomarker was clinically established B-type natriuretic peptide so that only two of the trials list novel biomarker evaluation as objectives. Because most of the phase I trials in other areas are done in healthy volunteers (13) wherein toxicity and safety assume a greater importance than target modulation and bioactivity, the comparison of biomarker usage in oncology phase I trials to nononcology phase I trials is difficult to assess.

NCI-sponsored phase I trials were more likely to include biomarkers than industry-sponsored trials. This finding reflects the emphasis that the NCI has placed on the development of novel biomarkers (14). The fact that industry sponsorship was not associated with inclusion of biomarkers with the same frequency as NCI sponsorship suggests that the industry did not place the same overall emphasis on development of biomarkers during this time frame. It is possible that the industry has increased its sponsorship of biomarker research more recently, and our study may not have detected this trend. There was no clear correlation between the value of biomarker utilization and sponsorship of the trial.

The finding that serum studies constituted the most common source of biomarkers suggests that easy accessibility, safety, relative inexpensiveness, and possibly patient acceptance of the required procedures for obtaining the samples are important factors in determining the practical utility of a biomarker. Tumor tissue was the second leading source of biomarkers and contributed primarily to a confirmation of mechanism of action and inhibition of target at doses achievable in humans. Normal tissue biopsies (e.g., skin, bone marrow, etc.) also represent a convenient source of biomarkers because they include sites that are more accessible than tumors but still provide cells and tissues in which the modulatory effects of drugs on molecular targets and pathways can be evaluated (15–17). Evidence from phase I trials of epidermal growth factor receptor–tyrosine kinase inhibitors, such as erlotinib, suggests that normal skin biopsies can serve as adequate tissue to show target inhibition by the experimental agent (17). However, clearly, this does not provide information as to whether the target was modulated in the malignant cells.

Toxicity and pharmacokinetics remain the main end points for dose and schedule selection for phase II studies. Our analysis of the contribution of biomarkers to dose selection in published articles revealed that they were useful in supporting dose for further studies in only 13% of the phase I trials. This support was mainly through demonstration of target inhibition at doses close or equal to the MTD. In only one study (1%) was biomarker information used as the primary determinant for further dosing in the absence of toxicity considerations (18). This finding is in agreement with a retrospective analysis of 65 phase I trials, in which toxicity and pharmacokinetics were the primary basis for dose recommendation in 67% and 21% of the trials, respectively (19). The reasons why biomarkers infrequently affected dose selection include the unclear relationship between dose and biomarker modulation, difficulty in

making a quantitative assessment of the biomarker, and significant interpatient and intrapatient variability in the results of biomarkers. Another possible reason is reliance on the paradigm that the highest dose tolerated should be used, regardless of the information from biomarker studies (20).

The fact that biomarker information, in the absence of MTD determination or efficacy information, primarily contributed to the proposed dose for additional study in only one published trial raises questions as to their actual value in this setting, especially for biomarkers (such as tumor biopsies) that have some potential risks for patients. Although optimal doses, or doses that provide maximal efficacy and acceptable toxicity for an experimental agent, often have to be further defined in phase II studies, phase I trials are critical for determining the initial dose level for testing in further studies. Biomarkers could potentially serve as "fine adjustments" for dose definition in phase I trials because they can potentially show maximal target inhibition at a dose below the MTD. Unfortunately, that did not happen in any of the articles included in this analysis. These concerns, along with the extra time, logistics, and effort required to obtain biomarkers can negatively affect the rate of accrual to trials. In addition, there is preliminary evidence that use of biomarkers may significantly increase the costs of phase I trials. A single institution retrospective analysis of 18 phase I trials conducted in the period of 1995 to 2002 showed that the budget cost per subject enrolled increased from $7,535 to $14,989 for trials that included biomarkers in their design compared with trials with no biomarkers (21). Therefore, the utility of biomarkers should be measured against their effect on costs, accrual, and especially patient safety. Highly expensive biomarkers and/or biomarkers requiring invasive procedures with potential for increased risks should not be included in clinical trials if the information provided by them will be unlikely to change decisions about further development of the experimental agent.

Biomarkers provided evidence supporting the proposed mechanisms of action of the studied compound in 34 of the 87 published trials (39%). Studies of mechanisms of action in early drug development can provide reassurance that the intended target is being modulated at a dose and schedule of the agent that are not too toxic. This may be an important consideration in the decision making to proceed with further development of that agent, particularly in the absence of clinical evidence of antitumor activity. To best help investigators predict early success or failure of new agents, it would be valuable to establish a correlation between modulation of the biomarker and improvement in clinical outcomes (22, 23). For example, lapatinib is an orally active dual erbB-1/erbB-2 tyrosine kinase inhibitor that inhibits both the epidermal growth factor receptor (also called erbB-1) and HER2/neu (erbB-2). Confirmation of inhibition of the erbB-2 protein motivated investigators to proceed with drug development for lapatinib based on clinical efficacy and evidence of HER2/neu inhibition obtained with trastuzumab (24). Unfortunately, none of the biomarkers in the articles reviewed for this study were validated as surrogates for important clinical outcomes, such as clinical response or delay in tumor progression, and we found no instances either in our study sample or in the literature of drug development termination based on biomarker results.

Tumor tissue biomarkers apparently have a higher rate of contribution to dose and confirmation of mechanisms of action (32% and 58% of the 19 studies) than other types of biomarkers. We did not perform a formal statistical analysis of the differences in rates of contribution between different types of biomarkers because the samples were considered too small. One possible explanation for the apparent superiority of tumor tissue biomarkers includes the fact that 6 of the 19 trials of tumor tissue biomarkers were gene transfection studies in trials of experimental gene therapy. Five of the six gene transfection studies played an important role for dose selection and for confirmation of mechanisms of action. This finding might have overestimated the value of tumor tissue biomarkers for other types of agents.

This analysis has limitations. First, the definition of biomarkers was broad and included a highly heterogeneous group of biological variables. Second, our analysis of contribution of biomarkers to phase I trials depended on interpretation of articles rather than primary data. We attempted to reduce the subjectivity of this analysis by having four independent investigators review the data and accepted their interpretation only when they had concordant opinions. Third, it is likely that there exists publication bias against biomarker-directed trials that found no drug effect on a target and therefore were not published. Similarly, there exists publication bias against trials in which the agent did not proceed to phase II evaluation. Another potential source of publication bias is the fact that we initially included published ASCO abstracts only. Rejected ASCO abstracts, abstracts that were withdrawn from ASCO for publication, and studies that were not submitted to ASCO do not participate in our analysis. Abstracts provided only limited information about biomarker results, and therefore, it was not possible to consistently analyze biomarker contribution from abstracts. Thus, our analysis may underestimate the importance of biomarkers in terminating a drug's evaluation. Fourth, this analysis does not include the most recent trials of the increasingly large numbers of targeted agents.

In summary, biomarkers comprise a heterogeneous group of new tests that have been incorporated into clinical trials with increasing frequency from 1991 to 2002. During this period, NCI sponsored trials, trials testing biological agents, and trials in adult populations were most likely to use biomarkers. Biomarkers made a minimal contribution to dose and schedule selection for phase II studies, but had greater effect in providing evidence confirming target modulation in human subjects. Our results suggest that acceptable toxicity and some evidence for antitumor effect remain the main end points used for decisions to proceed or not proceed with further drug development. Although there is a potential for biomarkers to positively affect new drug development, additional careful evaluation is necessary before this can be broadly achieved.

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