Cancer Therapy: Reimbursement of New Therapeutic Technologies

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New drugs and technologies for cancer treatment are being developed at a rate that has created a reimbursement crisis. This article discusses third-party concerns about this problem and describes generic criteria that have proven to be useful in assessing any new technology. It is equally important to discontinue funding of ineffective and obsolete therapies as it is to devise a strategy for identifying and encouraging the development of new therapy that will be both clinically useful and cost-effective. Examples are provided to show that these are not necessarily mutually exclusive goals. Off-label application of standard therapy as well as the funding of new cancer therapy are considered. High-dose chemotherapy with autologous stem-cell support for treatment of a variety of neoplasms has become a major reimbursement challenge. Other technologies such as autolymphocyte therapy and use of colony-stimulating factors are considered in detail. Finally, a process for deciding how to fund new cancer therapy is described.

The discussion in this paper is confined to reimbursement issues of cancer therapy in general, and as related to new therapeutic technologies. Inevitably, these concerns are linked to the broader problems associated with rising health care costs. Some of these critical issues are beyond the scope of our topic, but should be identified. For example, the enormous potential costs to third-party payers from litigation generated by denial of benefits for investigational therapy, as well as the influence of politics, and the power of lobbying groups on corporate coverage decisions deserve thoughtful, constructive solutions. Similarly, the effect of 35 million Americans without health insurance, of unemployment, poverty, and the irrational distribution of access to medical care on the national health budget are key issues that cannot be covered in a discussion of this sort. There is, however, a relentless force propelling medical costs upward that is clearly related to cancer treatment.

The rapid emergence of new technologies in health care in recent years has placed an enormous financial burden upon third-party payers. According to data from A. Foster Higgins, a benefits consulting firm, spending on company-paid health care

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Abbreviations: ABMT: autologous bone marrow transplantation ALT: autolymphocyte therapy AMA: American Medical Association DATTA: Diagnostic and Therapeutic Technology Assessment Division FDA: Food and Drug Administration G-CSF: granulocyte colony-stimulating factor GM-CSF: granulocyte macrophage colony-stimulating factor HDChx: high-dose chemotherapy IL-2/LAK: interleukin 2 plus lymphocyte-activated killer cells IND: investigational new drug MTD: maximum tolerated dose MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin PSCT: peripheral stem-cell transplantation RCC: renal cell carcinoma RCPT: repetitive conventional-dose therapy TIL: tumor-infiltrating lymphocytes TNF: tumor necrosis factor

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averaged in excess of $2,300 per employee by 1988, up 19 percent over 1987 levels. A current review by Tom Wicker [1] cites a rise in corporate medical benefits to $3,161 per employee in 1990, 44 percent more than in 1988. Even this figure is misleading, since the major cause of rising health care costs is the expense of caring for a small number of people (the expensive top 10 percent) with extremely severe medical problems. Annual costs for patients in this group soared to $10,529. In a study by Ohio's Blue Cross-Blue Shield, "50 people—victims of major, sometimes chronic problems like muscular dystrophy, cancer and mental disorders—alone required more in health care benefits than 40,000 of the people in the 90 percent requiring the least care" [1].

Although Wicker suggests that strategies such as "individual case management" and establishment of "centers of excellence" to negotiate fixed fees for expensive procedures may drive down current high costs of the kind of treatment needed by only a small number of patients, these programs, in fact, have been established and operative by private insurers for more than five years without significantly reducing the rise in medical costs.

One reason for the growth in expenditure is the increasing sophistication of medical science, a significant portion of which is investigational therapy. John Burry, Jr., chief executive of Ohio's Blue Cross-Blue Shield, asked recently, "Is it fair to allocate the astronomical costs of these quasi-experimental (in some cases) procedures and technology to the employer and/or the individual?" [1].

One view, held by those who have not assessed this problem critically, is that third-party payers should continue to fund these ever-rising costs. The AIDS epidemic has been largely responsible for bringing this problem to the forefront, as concerned individuals seek ways to assure that the afflicted have access to promising therapy at a time when spiraling cost has become an issue that can no longer be ignored [2].

The funding of investigational therapy is a societal problem that involves not only laboratory and clinical researchers, but also governmental agencies (National Cancer Institute, HCFA, Medicare, Medicaid), our elected representatives in the House and Senate, the Office of the Secretary of Health and Human Services, the pharmaceutical industry, the legal profession, corporations and businesses who are expected to pay all or a substantial part of the health care costs of their employees, as well as third-party payers. While reimbursement of investigational cancer care is the focus of this paper, costs will be incurred for the care of cancer patients whether treatment is considered standard or investigational. Since all parties involved are dismayed by rising health care costs, no one group can abdicate responsibility.

Dr. George P. Canellos posed the fundamental question succinctly. "A standoff has resulted, leading many to question: Who should pay for translation of laboratory science to the bedside?" [3].

Technology assessment by third-party payers focuses on three distinct areas: new technology, future technology, and firmly established technology.

**New**

The primary purpose of the assessment procedure is to determine whether the new technology is broadly accepted as medically necessary or is investigational or experimental. The process generally begins with a comprehensive review of medical literature describing tentative conclusions reached by scientific studies. Additional
information or evaluations can be solicited from federal agencies, medical specialty societies, other insurers, and manufacturers, as well as renowned professionals in their respective fields. The following set of criteria are useful to aid in the evaluation of new technology.

- Is there an appropriate rationale for the treatment?
- Is there evidence that the treatment is effective?
- Is there evidence that the treatment is harmful?
- Do the benefits justify the immediate and delayed risks of the treatment?
- Has the treatment been endorsed by the appropriate medical authorities, such as the Food and Drug Administration (FDA), the American Medical Association (AMA), or other medical specialty societies or specialists? Is the treatment being covered by Medicare or other public programs?
- Is the device or treatment the subject of ongoing investigation or research?
- Is the treatment only in use in a foreign country or by one provider?
- Is the treatment legal in this country?
- Have controlled clinical trials been carried out that demonstrate the treatment's efficacy?
- If there have been no controlled clinical trials, is the disease so rare as to render the requirement of controlled studies inappropriate? If so, is the treatment safe?
- Are there appropriate indicators that may be used to identify those patients who are likely to respond and those who will not? If so, under what conditions is this treatment appropriate?
- Is this treatment or technology the only one available to achieve the desired outcome, or are there other related treatments or technologies that provide an identical outcome in a more cost-effective manner?

**Future**

Future technology should be handled in very much the same manner as new with respect to reviewing the medical literature. It is often premature, however, to apply the “broadly accepted” test because not enough scientific studies have been completed. In such instances, the initial findings should be documented and the topic placed on a tracking list for future review and to follow its development.

**Firmly Established**

On occasion, previously reviewed technology, which has been broadly accepted as medically necessary, is subsequently challenged as to its effectiveness, based upon new evidence. In such instances, the process of intensive literature review is undertaken, and positions taken by pertinent agencies and/or societies relevant to the questionable technology are solicited. If the therapy is now determined to be obsolete, it should no longer be considered appropriate for coverage by third-party payers.

In applying these evaluation criteria to specific cancer treatments, a reasonable “gold standard” for any drug for insurance coverage would seem to be FDA approval. Although this status appears to be a criterion that logically cannot be challenged, the author recently had an experience regarding a drug (interleukin 2) that had been denied FDA approval on the basis of insufficient clinical data. The drug had nevertheless been administered to an insured with cancer, and coverage was denied. This denial of benefits was challenged by the insured, who appealed
through the offices of the Texas State Legislature. A senator, who had no medical expertise, dismissed out of hand lack of FDA approval as a valid reason for denial of benefits! It is unlikely that this view would find widespread support in the scientific community. Another related issue in the case: what would be the liability of the third-party payer for damages if the insured were harmed by a non-FDA-approved drug that was reimbursed by the insurer?

The process necessary to obtain FDA approval for a new drug is tedious and expensive, usually requiring several years at a cost of millions of dollars. To facilitate access to new drugs, currently class C classification of a drug by the National Cancer Institute or treatment investigational new drug (IND) status by the FDA, identifies promising treatments that are put on an accelerated pace of investigation at certain identified institutions. Reimbursement for such special categories by third-party payers (Medicare, Medicaid, private insurance) is an issue requiring serious consideration. In this context, payers should identify centers of excellence which would be appropriate sites for covered use of drugs in these special categories. Reimbursement for the use of other investigational drugs, as recommended by the Lasagna Committee [2], should be considered if such use has been approved by expert government agencies, in authoritative medical compendia, or by a committee established by the Secretary of Health and Human Services. The Lasagna Committee also suggested: (1) use of the treatment IND earlier in the drug development process where alternative therapies are unavailable, and (2) expanded access (parallel track) IND to investigational drugs when there is assurance that adequate clinical trials are in progress and will not be compromised.

Off-label use of FDA-approved drugs is commonly practiced by medical oncologists. If such off-label use proves to be effective, prompt publication of results in the peer-reviewed literature will facilitate third-party reimbursement. As a practical matter, a major insurance carrier, processing millions of claims every week, cannot identify off-label use of approved drugs unless the dollar amount becomes high profile. In addition, it is not cost-effective for the pharmaceutical industry to expend the dollars and effort to gain FDA approval for indications not included in the initial labeling if such use is already widespread and reimbursed.

The most widely publicized “standoff” between payers and clinical investigators has been over the use of high-dose chemotherapy (HDChx) followed by autologous bone marrow transplantation (ABMT) for a number of disseminated cancers, particularly carcinoma of the breast.

When I first assessed this technology in 1988, it was clear that it was an emerging new technology that appeared still to be investigational and not reimbursable under the contract language, which defined covered treatment as “broadly accepted as medically necessary.” Several experts in the fields of medical and radiation oncology who were contacted by the author at that time (1988) regarding HDChx and ABMT for breast cancer emphatically agreed that this was still an investigational treatment.

In 1988, I conducted a comprehensive technology assessment of HDChx and ABMT, considering not just breast cancer but its use for all neoplasms. Not only did this strategy have a high dollar cost ($40,000 to $70,000 per transplant) but it also was associated with a number of scientific questions that remained to be answered. If the patient’s marrow already contained tumor cells, did it need to be “purged” of these cells before reinfusing, and, if so, what was the optimum technology for purging? At that time, there was a substantial risk associated with ABMT: 10 percent mortality,
10 percent failure to recover normal blood counts within two months of the treatment, and severe, major life-threatening toxicity in up to 15 percent of patients. It was not clear who should be treated with the regimen. The available information in 1988 suggested that this regimen salvaged some patients, but the data were not mature [4–10].

There was, at that time, an appropriate rationale for this technology and early evidence that it was effective in a fraction of the patients treated. There was, however, no generic official endorsement of treatment, and no controlled clinical trials were available. The potential toxicity was apparent, and it was not clear that the treatment outcome outweighed the risks.

Over the course of the next year, although there were no controlled clinical trials, new published studies demonstrated successful and long-term survival in some patients with relapsed Hodgkin’s disease, non-Hodgkin’s lymphoma, stage III and IV neuroblastoma, and second-remission acute leukemia. Mortality and morbidity associated with HDChx remained substantial, but, with no other therapeutic options available, the potential benefit appeared to justify the risk. The issue of marrow purging remained unresolved, but disease-free survival following infusion of unpurged marrow in these four diseases suggested that purging might not be a critical issue. Therefore, early in 1989 I recommended coverage for HDChx with ABMT for the four neoplasms specified above. Independently, the National Center for Health Services and Health Care Technology Assessments published a position paper that officially endorsed HDChx with ABMT for the above diseases, but at the same time indicated that the data did not support the use of this technology for other tumors.

During 1990 and early 1991, an increasing number of requests were made by providers for reimbursement for HDChx and ABMT for patients with breast cancer in a variety of stages and situations. The author searched the literature extensively, but other than individual, and usually small, series from a variety of institutions, there were no published controlled clinical trials to verify the efficacy of this strategy in the treatment of breast cancer and no parameters to identify patients who would be suitable candidates for HDChx and ABMT [11–27]. Reimbursement was denied, relations with providers became acrimonious, and litigation was increasing as time went on. Not surprisingly, when individual cases came to court, a favorable judgment for third-party payers was impossible to obtain, in spite of lack of controlled clinical trials. How could a medically unsophisticated judge deny treatment to a patient eventually doomed to die of breast cancer, particularly if the afflicted insured appeared in his courtroom? Likewise it became equally impossible to obtain a favorable judgment (for third-party payers) to deny coverage of treatment that had been given with the mutual consent of payers and insured (with the monies held in escrow, pending outcome of litigation) on the understanding that such litigation would take place post facto so the patient could proceed with treatment without delay and the legal questions debated in a less emotionally charged environment. Once again Dr. Canellos’s “standoff” was apparent.

A number of actions were subsequently undertaken by clinical investigators and some third-party payers. Controlled clinical trials are under way in both a multi-institutional joint study sponsored by the Philadelphia Bone Marrow Transplant Group (Protocol PBT-2) as well in South Western Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG) trials. Also, Blue Cross-Blue Shield agreed to reimburse this treatment for breast cancer patients entering controlled
trials: that approval, however, applied to some but not all Blue Cross-Blue Shield plans. This approach raised two interesting questions. First, why should a payer reimburse for specific cancer therapy for some of its insureds, while denying coverage for insureds enrolled in other Blue Cross-Blue Shield plans not included in the study groups? Second, how to answer serious questions raised by those patients entering clinical trials? Some would be required to enter a control arm that denied access to a now well-publicized treatment for breast cancer.

More recently [28], the DATTA (Diagnostic and Therapeutic Technology Assessment) group at the AMA re-reviewed ABMT and generally agreed that as an adjunct to HDChx it appeared to be no longer investigational, with the exception of marrow purging techniques. Their report, however, did not include a consideration of the efficacy of HDChx in breast cancer.

In 1991, as a result of troubling reimbursement issues surrounding the treatment of breast cancer with HDChx and ABMT, even though controlled clinical trials were as yet not completed and reported, several third-party payers opted for coverage of patients after individual review by a medical director.

Having done this, it remained to develop criteria to identify breast cancer patients suitable for HDChx and ABMT: criteria that would be acceptable to the clinical community as well as to nationally recognized peer-review organizations. After a review of the literature and critique by a DATTA panelist at AMA, I identified criteria (Table 1) [29–37], and evidence tables were constructed (Table 2) [38–44]. At this time, we recognized both ABMT and peripheral stem-cell transplantation (PSCT) as equally acceptable and effective technologies, particularly since PSCT would allow breast cancer patients with insufficient or contaminated marrow to be treated with HDChx.

In the evidence tables for patients with stage II and stage III breast cancer at high risk of relapse (ten or more involved axillary nodes), relapse-free survival data show a clear advantage for HDChx and ABMT at three and five years. In patients with stage IV breast cancer, comparing repetitive conventional-dose chemotherapy with single high-dose treatment and ABMT after standard induction chemotherapy, complete remission rates are 10 percent and 58 percent, respectively, and median response and survival durations impressively lengthened in the group receiving standard induction chemotherapy followed by HDChx and ABMT.

In addition to breast cancer, third-party payers will need to conduct ongoing research pertaining to clinical effectiveness and reimbursement issues related to HDChx and ABMT or PSCT, since additional cancers appear to be likely candidates for the treatment with requests for coverage by providers. Some of these include ovarian cancer, small cell carcinoma of the lung, plasma cell myeloma, refractory testicular carcinoma, and refractory, metastatic Ewing’s sarcoma.

The need for continuous assessments is illustrated by my experiences during an episode that occurred last year. A request for reimbursement for treatment of a patient with testicular cancer with HDChx and ABMT was initially denied, and then erroneously approved by Aetna in 1991. Since the treatment was certified, even though in error, payment was made without question. The case, however, became the topic of a prominent television news magazine program, providing a glaring example of exploitation by a medically unsophisticated news medium of the “Canellos standoff” on the topic of who should pay for the translation of laboratory science to the bedside. Not only did my literature review at that time fail to provide sufficient
TABLE 1
Patient Selection Criteria

Stage II and III Breast Cancer

A. Acceptable: patients who have received neo-adjuvant cytotoxic chemotherapy and have an adequate hematologic status (white blood cell count > 4,000 mm³ and unmaintained platelet count of 100,000 mm³)
B. Age: not more than 60 years of age
C. Performance status: ECOG 2 or better; Karnofsky 60—70 or better
D. No history of second malignancy or patient free of disease for five years; resected non-melanomatous skin cancer or carcinoma in situ of uterine cervix are not exclusion criteria
E. Negative HIV serology
F. No severe pulmonary disease; exclusion criteria: carbon monoxide diffusion capacity, less than 50 percent predicted; FEV₁ (forced expiratory volume in one second), less than 50 percent predicted; PAO₂, less than 60 mm Hg (torr)
G. MUGA: 50 percent ejection fraction or better in patients receiving cardiotoxic agents
H. Renal function adequate, as defined by: serum creatinine, not > 1.8 mg/dl, and creatinine clearance, at least 40 ml/minute
I. Liver functions adequate, as defined by: serum bilirubin not > 2.0 mg/dl; SGOT not > two times normal
J. Patients with stage II disease with ten or more positive axillary nodes are acceptable
K. If patient has less than but six or more positive axillary nodes, she may be considered an appropriate candidate if pre-menopausal, estrogen receptor- and progesterone receptor-negative, and meets criteria B through I
L. Inflammatory breast cancer or patients with locally advanced breast cancer, who, after loco-regional therapy alone (surgery, with or without RT) show microscopic residual disease in the resected specimens are acceptable
M. Therapy to begin within eight weeks of surgery for the primary breast cancer

Stage IV Breast Cancer

A. Acceptable: patients with metastatic disease who fail to achieve at least partial remission after three cycles of initial standard chemotherapy and if estrogen receptor- or progesterone receptor-positive, also failed trial of endocrine therapy, with adequate hematologic status (white blood cell count > 4,000 mm³ and unmaintained platelet count of 100,000 mm³)
B. Also acceptable: patients who have relapsed less than a year after surgery for the primary breast cancer and adjuvant chemotherapy and have adequate hematologic status as defined above
C. Age: no more than 60 years of age
D. Untransplanted life expectancy of at least six weeks or more
E. Performance status: ECOG 3 or better; Karnofsky 40—50 or better
F. No history of second malignancy unless free of disease for five years, except for resected non-melanomatous skin cancer or carcinoma in situ of the uterine cervix
G. Negative HIV serology
H. No severe pulmonary disease; exclusion criteria: carbon monoxide diffusion capacity, less than 50 percent predicted; FEV₁, less than 50 percent predicted; PAO₂, less than 65 mm Hg (torr)
I. MUGA: 50 percent ejection fraction or better in patients receiving cardiotoxic agents
J. Renal function adequate, as defined by: serum creatinine, not > 1.8 mg/dl, and creatinine clearance, at least 40 ml/minute
K. Liver function adequate, as defined by: serum bilirubin not > 2 mg/dl, and SGOT not > two times normal
L. Abnormal renal and liver functions criteria not cause for exclusion when secondary to organ involvement by metastatic disease
M. Sites of disease: acceptable are patients with less than three sites of disease. (Sites of disease are: [1] soft tissue, [2] visceral, and [3] bone.) More than one metastasis in one site does not equate to greater than one site. In order to include patients with advanced disease as defined by sites whose functional impairment is less than might be expected, acceptable are patients with three sites of disease who have a performance status of ECOG 2 or Karnofsky 60—70.
N. Estrogen receptor status: acceptable are estrogen receptor- and progesterone receptor-negative patients; or estrogen receptor- or progesterone receptor-positive patients who have hormonally refractory breast cancer
O. No intracranial metastases
P. Patients who receive standard induction chemotherapy should be responsive to the chemotherapy administered prior to high-dose chemotherapy and autologous bone marrow or peripheral stem-cell support
TABLE 2
Evidence Tables for High-Dose Chemotherapy with ABMT for Breast Cancer

| Therapy                      | No. of Patients | 1 Year | 3 Years | 5 Years |
|------------------------------|-----------------|--------|---------|---------|
| Standard-Dose Regimens       | 813             | 58-92  | 23-56   | 13-45   |
| HDChx + ABMT                 | 53              | 96     | 80      | 79.4    |

Stage IV Breast Cancer:
Response to Repetitive Conventional-Dose Therapy (RCPT) versus Single High-Dose Treatment and ABMT after Standard-Dose Induction Chemotherapy (HD + AT + IC)

| Therapy     | No. of Patients | Complete Remission (%) | Response Duration | Survival Duration |
|-------------|-----------------|------------------------|-------------------|------------------|
| RCPT        | 3,734           | 373 (10)               | 7.6               | 13.9             |
| HD + AT + IC| 381             | 221 (58)               | 19 (estimated)    | > 21             |

Data to document the efficacy of HDChx and ABMT for testicular cancer, examination of the patient-specific clinical information showed that the treating physicians had chosen this therapeutic intervention before all standard chemotherapeutic regimens had been applied to the treatment of the patient's neoplasm. The sensitivity of embryonal cell carcinoma of the testis to many standard chemotherapy options, resulting in cure, is well known by medical oncologists. Application of an investigational, as yet unproven, treatment strategy before all standard chemotherapy regimens had been reasonably applied does not appear to be responsible medical practice. In spite of being apprised of the lack of medical logic in this particular case, the news medium insisted upon televising their original story, blaming the third-party payer for originally denying what was clearly investigational therapy, also implying that the patient was harmed by a "delay" in treatment. The fact that standard therapy was withheld while awaiting approval for investigational therapy was ignored in the television presentation. When the story was rerun in July 1991, there was still no reference to the actual clinical facts which had previously been personally presented to them.

New technologies continue to be developed and introduced rapidly into clinical practice. For example, we reviewed the literature on extracorporeal photopheresis for cutaneous T-cell lymphoma in 1989 and concluded that, since this treatment was both safe and effective, it should be a covered benefit. Similarly, total electron beam irradiation for severely generalized skin involvement in this disease (mycosis fungoides) appears to be preferable to topical nitrogen mustard application when given in centers with the special facilities able to satisfy the demanding technical aspects of this therapy. It should be a covered benefit under these conditions. On the other
TABLE 3
Treatment Options for Metastatic Renal Cell Carcinoma: Median Survival

| Treatment                                      | Median Survival (months) | Reference |
|------------------------------------------------|--------------------------|-----------|
| Natural history                                | 6.0                      | [43]      |
| Conventional chemotherapy                      | 7.0                      | [43]      |
| IL-2/LAK+                                     | 6.2                      | [52]      |
| IL-2 + beta interferon                         | 7.2                      | [51]      |
| IL-2 + mitogen-activated autologous lymphocytes | 10½ maint.               | [52]      |
|                                               | 16½ maint.               | [52]      |
| Interferons                                    | 8–10                     | [53]      |
| Interferon beta serine                          | 7.5                      | [54]      |
| Interferon gamma                               | 8.5                      | [55]      |
| Interferon alpha + prednisone                  | 11.0                     | [56]      |
| Interferon alpha + gamma                        | 9.3                      | [57]      |
| Interferon + chemotherapy                      | 8–10                     | [58]      |
| TIL                                            | ID                       | [59]      |
| TNF                                            | ID                       | [60]      |
| ALT                                            | 21.0                     | [47,48,49]|

*Median response duration to date of publication
ALT, autolymphocyte therapy
ID, insufficient data
TIL, tumor-infiltrating lymphocytes
TNF, tumor necrosis factor

hand, hyperthermic treatment of deep-seated, non-cutaneous cancers has yet to be proven effective by controlled clinical trials and should not be reimbursed.

Now the era of immunotherapy for cancer has arrived, with reimbursement issues already commanding thoughtful consideration and research by third-party payers. Some of these therapies will undoubtedly be initially promising, and requests for insurance coverage for very new or investigational treatments should be expected by insurers, who will need to be ready with well-thought-out answers. As an example, consider autolymphocyte therapy (ALT). Since this is a biological therapy, using the patient's (or donor) cells, FDA approval will not be needed.

Basically, ALT involves harvesting lymphocytes from a cancer patient, activating these cells to become cytotoxic, and subsequently reinfusing them into the patient. Toxicity has been minimal, in contrast to some other immunotherapies, such as interleukin 2 plus lymphocyte-activated killer cells (IL-2/LAK) therapy. ALT is currently being investigated only for the treatment of metastatic renal cell carcinoma (RCC), since this type is a neoplasm notoriously resistant to standard single-agent or combination cytotoxic chemotherapy. Median survival of untreated disease is approximately six months, with less than a 10 percent two-year survival. With standard agents, such as adriamycin plus cyclophosphamide, median survival is about seven months [43]. Some therapeutic options for metastatic RCC include: no therapy other than palliative measures, conventional chemotherapy, interferon alone or in combination with chemotherapy, investigational treatment with interleukin 2 plus lymphocyte-activated killer cells (IL-2/LAK), tumor-infiltrating lymphocytes (TIL), tumor necrosis factor (TNF) alone or in combination with chemotherapy, and, finally, the therapy under consideration: ALT [45–60]. Table 3 summarizes all options and provides median survival times in months for each.
Based upon a review of the literature and comparison with other therapies, ALT of RCC appears to be promising and merits serious consideration for coverage by third-party payers, although the firm data is derived from the most recent study, which involved only 36 patients. Certainly this treatment, which involved six outpatient treatments costing $2,000 each (total, $12,000) with no hospitalization, is much more cost-effective (as well as safer and less toxic) than treatment with IL-2/LAK, which usually involves a median two-week hospital stay, often in an intensive care unit, and has a 3 to 5 percent treatment-related mortality. ALT therapy also invokes an additional, unique approach: the concomitant oral administration of cimetidine, which inactivates suppressor cells within the patient that might otherwise block the resultant anti-tumor response. In summary, ALT, by combining specific in vitro immunization with anti-suppressor cell treatment, results in a novel and improved method of adoptive immunotherapy. Significantly, the quality of life during therapy, as indicated by an ECOG performance status of three or better until about two months prior to death, was favorable and may be translated into reduced health care costs during the period of remission.

Since the third-party payer assumes part or all of the reimbursement liability for the health care costs of a patient with RCC—ethical considerations aside—it may well be equally or more cost-effective to fund an early promising therapy such as ALT, rather than to fund standard chemotherapy, which is not likely to provide significant clinical benefit.

Finally, another new technology has emerged, requiring careful study by third-party payers as they consider appropriate reimbursement criteria: colony-stimulating factors [61-65]. In February 1991, granulocyte colony-stimulating factor (G-CSF) was approved by the FDA for the labeled indication "to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with significant incidence of severe neutropenia and fever." Subsequently, on March 5, 1991, granulocyte macrophage colony-stimulating factor (GM-CSF) received FDA approval. Labeling stated that it "is indicated for use in patients with non-Hodgkin's lymphoma, Hodgkin's disease and acute lymphoblastic leukemia who are receiving autologous bone marrow transplants" (not peripheral stem-cell transplants).

Although the much broader labeling indications for G-CSF than for GM-CSF have created controversy and confusion, many oncologists consider this instance to be more a reimbursement challenge than a true clinical distinction. It is believed that eventually G-CSF and GM-CSF will be approved both for the amelioration of febrile neutropenia associated with myelosuppressive chemotherapy and for the acceleration of recovery after bone marrow transplantation.

At present, there appears to be no question that co-administration of G-CSF with myelosuppressive therapy will improve the likelihood that patients will be able to tolerate chemotherapy cycles on schedule. This outcome is generally accepted by medical oncologists as desirable, since dose reduction or cycle lengthening due to leukopenia reduces dose intensity. A group of patients with advanced bladder cancer were treated at Memorial Sloan-Kettering Cancer Center in New York City with G-CSF combined with the MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin) every three weeks for four or five cycles. Historically, less than a third of patients have been able to tolerate the MVAC regimen on schedule because of
myelosuppression and low neutrophil counts. With the addition of G-CSF for seven days after each cycle, 100 percent of patients were able to go on the next cycle [64].

Whether it will be possible to escalate doses of chemotherapeutic agents in conjunction with G-CSF and achieve clinically effective results is the subject of ongoing trials. Although the use of colony-stimulating factors may shorten the duration of neutropenia to a period of six to eight days, its depth may well be unchanged. It is recognized that the more chemotherapy given, the more the supply of cells that can respond to growth factors is depleted. Patients still are subject to prolonged nadirs when cell counts are low. The maximum tolerated doses (MTDs) that have been established for standard chemotherapy agents over the last 30 years are based on the numbers of stem cells left in the bone marrow after treatment. Growth factors have not changed those numbers: it is not possible to escalate beyond the MTD because the population of cells that can respond to growth factors has been eliminated [64].

Turning to clinical studies of GM-CSF [61,62], the treatment of patients with this factor following ABMT results in fewer days of infection and improved white blood cell counts compared to untreated patients. As a result, these patients needed fewer antibiotics and, in some cases, shorter hospitalizations. Side effects associated with moderate doses of GM-CSF have generally been mild and easily managed. In clinical trials, diarrhea, skin rash, weakness, and malaise were found in only 5 percent more subjects treated with GM-CSF than in the placebo group [65]. More serious toxicity associated with GM-CSF has been reported and includes myalgias, bone pain, low-grade temperature, flushing episodes, pericardial effusions, and serositis-type episodes. These, however, appear to be dose-related: subsequent studies using lower doses of GM-CSF have been shown to be equally effective and not associated with significant toxicity [64].

An important issue that still remains unresolved is whether the dose escalation of cancer chemotherapeutic agents facilitated by the use of colony-stimulating factors will result in the appearance of non-hematologic toxicities such as cardiac, pulmonary, central nervous system, and gastrointestinal types.

Also, neither G-CSF nor GM-CSF exert any beneficial effect on platelets and may actually have some adverse effect on platelet counts. Whether the mild thrombocytopenia is clinically relevant remains to be studied. This lack of effect on thrombocytes has stimulated research into the newer cytokines, such as IL-3, stem-cell factor, and the "pixie molecule" (combination of IL-3 plus GM-CSF), all of which may have specific effects on platelets.

Cost efficacy represents another area of uncertainty. Higher-than-usual dose chemotherapy followed by G-CSF will result in a shorter period of neutropenia, but it has been observed that prophylactic antibiotics may be just as effective and less costly. In the setting of bone marrow transplantation, however, there appears to be a consensus that appropriate use of GM-CSF should result in reduced overall costs. Dr. James O. Armitage, of the University of Nebraska School of Medicine in Omaha, Nebraska, has been quoted as saying, "Investing $3,000 in a drug that prevents a $20,000 hospital stay seems quite cost-effective [64]."

Other studies support the use of CSFs [65]. In one study of GM-CSF at the Fred Hutchinson Cancer Research Center in Seattle, the average hospital stay for patients with successful marrow transplants was reduced from 43 days to 28 days, and average treatment cost fell from $112,000 to $79,000.
In a multi-center, double-blinded, randomized, placebo-controlled trial of patients treated with cancer chemotherapy, those receiving G-CSF required 50 percent fewer hospitalizations for febrile neutropenia than those who did not receive the agent. The amount saved per cycle of chemotherapy ranged from $753 to $5,117 and appeared to be related to the patient's health insurance (Medicare versus private) and among different hospitals. Medicare program savings ranged from $1,007 to $1,638.

How, then, should new technologies for cancer therapy be reimbursed? Off-label use, new technologies endorsed by "gold-standard" organizations (like DATTA) applied in cancers for which other treatments are available and more cost-effective, new technologies that appear promising and potentially cost-effective but not yet reviewed by an unbiased panel of experts all may require simple or enormously complex technology assessments in order to arrive at a logical, defensible, and, it is hoped, cost-effective reimbursement policy by third-party payers.

The decision process would involve literature review and expert panel consultation. Clearly, if a treatment is already established as effective and broadly accepted, there is no reimbursement issue and coverage should be certified. Unfortunately, investigational therapy is often not clearly defined in standard contract language. What constitutes investigational therapy may become a legal rather than a clinical issue. These considerations notwithstanding, if a new technology is identified as investigational, literature review and consultation with an expert panel are necessary to arrive at a coverage decision.

New technologies that are investigational but deemed promising by this review process should be eligible for reimbursement; this payment should include all reasonable costs associated with treatment of the cancer patient. On the other hand, investigational therapy identified as not promising after literature review and impartial panel assessment should not be covered. Ideally, this decision process should also incorporate a method to review both old as well as new technologies, in order to identify ineffective or obsolete treatments that should no longer be eligible for coverage.

This route appears to be a rational approach to the issue of reimbursement of cancer therapy by third-party payers. The examples provided should have made the following problems and goals clear:

This effort can be a complex, ongoing endeavor.
A significant investment of time, personnel, and funds are required.
The reimbursement decision must be considered fair by the practicing community of oncologists.
The reimbursement decision should be cost-effective.
The process should result in significant reduction in the rising rate of health care costs.
The process should include a method of discontinuing reimbursement of ineffective or obsolete technology.
The process should encourage development of promising new treatments.

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