Improving the Balance between Treatment and Diagnosis: A Role for Radioimmunodetection

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Abstract

Despite major advances in diagnostic testing, including the introduction and widespread availability of high-resolution computed tomography (CT) and magnetic resonance imaging, inadequate diagnostic information still interferes with proper management of many patients with cancers. This is particularly true for recurrent colorectal cancer, for example. In the course of this symposium, significant advances have been reported which are likely to improve management of this clinical situation. $^{111}$In oncoscint for colorectal and ovarian cancer imaging, has been approved for single use only, and is a product licensed by the Food and Drug Administration. It has been shown to be significantly more effective than CT for detecting the presence of disease that is confined to the abdomen outside the liver. This agent is very useful in a limited role. A larger opportunity awaits other preparations reported at this conference, especially $^{99m}$Tc-labeled Immuno-4 carcinoembryonic antigen, which is significantly better than CT for determining resectability of recurrent cancer (T. Behr et al., Cancer Res. 55 (Suppl.): 777S-78Ss, 1995). The $^{99m}$Tc-labeled compound preparations offer the advantages of low immunogenicity, excellent imaging energies of $^{99m}$Tc, and “same-day” imaging.

Even the most effective cancer treatment such as surgical resection, if applied to a patient who basically does not need it, can be a needless expense and a trauma to the patient. To date, our emphasis in oncology research has been heavily weighted toward developing new therapies. The success of radioimmunodetection is one indication of why it is time for a paradigm shift, during which we can move toward a more balanced program that emphasizes both diagnosis and therapy. To achieve this we must urge research institutions such as the National Cancer Institute and American Cancer Society to make major investments in the diagnostic aspects of cancer care. With the knowledge base that we have now, we can make improvements in patient care by emphasizing development of improved diagnostic methods and support for cost-effectiveness studies for developed methods, in order that currently available treatments can be more intelligently applied.

Introduction

In the past decade, we have seen a rapid advance in our understanding of the biology of cancer. For example, colorectal cancer requires a series of cumulative genetic insults to become malignant, and, during one crucial step, a tumor suppressor gene is somehow disabled and a defective p53 protein is produced (2). The chromosomal location of familial cancers such as retinoblastoma, colorectal cancer, and breast cancer has been determined. A number of oncogenes have been described which promote tumor growth. Examples include the epidermal growth factor receptor and transforming growth factor α and β angiogenesis factors. The predominant causes of multidrug resistance are the P-glycoprotein transporter molecules and topoisomerase mutations. In short, there has been an explosion of knowledge at the basic science level in terms of the causation of cancer. One day these advances in basic knowledge will be translated into improved cancer treatment, but truthfully that day is a considerable distance away, probably after the turn of the century.

In contrast, in terms of patient outcomes, oncology practice has changed little in the recent past. That is not to say that there have not been some improvements. In the way of drugs, Taxol and its derivatives and also the retinoic acid agents have been successful improvements. MRI and CT had a major impact early in this period, especially for spinal disease (MRI). The influence of these modalities has clearly plateaued, and we are still left with serious problems of patient management both in terms of diagnosis and treatment. But these advances have been gradual, stepwise, and incremental rather than a quantum step, and we in the practice of medicine have to admit that the cancer patient is only slightly better off today than he or she was 10 years ago.

Maximize the Benefits of Current Therapies through Improved Diagnostic Methodologies

The most important practical problem in oncology today relates to improper treatment planning based on inadequate diagnosis of the grade and stage of an individual patient’s tumor. As a result many patients receive either too much or too little treatment. For example, difficulties in diagnosis of recurrence sites in colorectal cancer hamper the surgical resection of hepatic and pelvic metastases. The staging of the non-small cell lung carcinoma is markedly limited by the relatively low sensitivity of current methods for distinguishing benign from malignant solitary nodules and for detecting mediastinal spread; this results frequently in unnecessary staging thoracotomies, with the resulting pain and expense of a major operation. Patients with breast cancer currently require a staging lymphadenectomy for prognostic reasons and to direct treatment. Improved methods for diagnosing lymph node spread would obviate the need for this painful operation that is associated with serious morbidity in a significant group of patients. Improved assessment of lymph nodes in early stage prostate cancer patients being considered for total prostatectomy would lead to more appropriate patient selection for a procedure with considerable morbidity, even in the best hands. In summary, misdiagnosis as to local extent and stage of the most common cancers is responsible for inadequate or excessive therapies.

In fact, more than one half of the patients with cancer have metastatic spread of their cancer at the time they are first seen by their physician, but this is rarely recognized clinically, and, as a result, inappropriate treatment is applied to many patients. Although this fact is widely known, support for diagnostic developments has lagged far behind support for basic science and development of new therapies. In part, the justification for this has been based on two arguments: (a) the companies should do diagnostic research, and (b) there are too few leads to follow for novel diagnostic methodologies with the required sensitivity and specificity.

These arguments are no longer persuasive. In the first place, clinical trials of the type required for Health Care Financing Administration funding of Medicare reimbursement are becoming increasing lie sophisticated and go well beyond what is required of companies for marketing of new instruments. Also, with the emergence of Health Maintenance Organizations and managed care, the diagnostic imaging manufacturers find that sales of expensive technology have plummeted, and there is very little money for support of large clinical trials.

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3 The abbreviations used are: MRI, magnetic resonance imaging; CT, computed tomography; RAID, radioimmunodetection.
Also, there have been enormous developments in new diagnostic methodologies in the last 15 years, including spiral CT, MRI, positron emission tomographic scanning, and certainly RAID. The clinical application of these methodologies, if done on the basis of adequate and well-controlled clinical trials, will change the face of American medicine in a way that is likely to reduce overall costs and increase treatment benefits.

In particular, nuclear medicine will have much to offer in the next decade. Positron emission tomography, fusion imaging, and of course RAID. As an aside, the three-dimensional radiological methods, such as CT and MRI, are excellent for imaging normal tissues and for defining the anatomy in the region of the tumor. But in terms of evaluating the tumor itself, these diagnostic methods depend on enlargement of normal structures, such as lymph nodes or an alteration in the signal from the normal tissues. This results in missed tumors, if nodal enlargement is absent or minimal. On the other hand, RAID actually principally images the tumor, detecting through the tracer principle, a subcellular target, the tumor-associated antigen at the nanomolar level. It is this ability to directly image the tumor that offers the greatest advantage of RAID over more conventional techniques. RAID has the potential for improving the diagnostic work-up of the cancer patient, especially in terms of detecting new sites of otherwise occult tumors, and appropriately distinguishing abnormal appearing regions that might be benign from tumors deposits.

RAID has demonstrated proof of principle as a method capable of diagnosing occult disease. Limitations that have been encountered in clinical practice include the development of human antimouse antibody, which interferes with repeated use of these agents, and low image contrast between tumor and surrounding normal structures. The recent experience in the interval since the last conference continues to show steady technical progress in overcoming these limitations. A number of reports of RAID has emphasized the benefits of 99mTc, with its ease of use and excellent imaging properties. In particular, when applied with antibody fragments, with its more rapid clearance from normal tissues, 99mTc offers excellent physical features of half-life. Also, the 99mTc fragments are also much less immunogenic than IgG preparations. There is a continued emphasis on the use of anatomical images in combination with RAID (fusion images). This has been shown to reduce the incidence of false positives, e.g., with 99mTc labeled NRLU-10, uptake in involved lymph nodes versus blood vessels. The advent of genetic engineering promises to result in optimized carrier molecules with even better targeting properties than IgG or enzymatically prepared fragments.

A Pivotal Trial in RAID Effectiveness in Colorectal Cancer

Carl Pinsky of Immunomedix reported on the clinical utility of a 99mTc-labeled Fab' fragment in patients with colorectal cancer (3). In this large study, 382 patients were entered into a Phase III study. Minor self-limited side effects were reported in 7 patients, and human antimouse antibody appeared in 1 of 240 patients after one injection and of the 18 patients who had received two injections. In patients with known disease, the prediction that a patient was resectable was 81% for RAID and only 64% for conventional diagnostic methods, including CT. In making the decision about unresectability, the decision was correctly made in 89% of the RAID patients and only 75% of the patients with conventional diagnostic methods. Overall, the conclusions of this study were that RAID was safe, allowed same-day imaging, induced little human antimouse antibody, and appeared to offer new information, either alone or in conjunction with conventional imaging methods, in terms of (a) the presence of occult disease and (b) the resectability of the patient.

An Important Staging Role for RAID in Lymphoma

The role of radiolabeled antibody in the detection of lymphoma was evaluated by Drs. W. Becker (Nuremberg, Germany; Ref. 4) and M. J. Blend (University of Illinois, Chicago, IL; Ref. 5). Both of these groups found considerable utility for 99mTc-labeled LL2 monoclonal antibody fragment for the detection of location and stage of non-Hodgkin’s lymphoma. This preparation appears to show excellent localization properties for staging lymphomas, and in a direct comparison to 67Ga citrate, was significantly better for lower grade lymphomas. If this can be confirmed in additional trials, this would be a major advance in staging since the proper staging of the low-grade lymphomas is notoriously difficult.

Success of Somatostatin-directed Radioligands

Finally, 111In octreotide was featured in a series of articles by the group from Uppsala, Sweden. Of course, octreotide is a somatostatin-directed agent, and therefore has a relationship to antibodies which also target specific antigenic sites on the tumor surface (6). In carcinoid tumors, the overall sensitivity was 82%, which is somewhat lower than that of previous reports. This seemed to be related to the fact that foregut, midgut, and hindgut tumor origin was associated with a widely varying sensitivity of detection. Only 38% of foregut tumors were positive, whereas 100% of the hindgut tumors were detected.

Of considerable interest was the finding that in patients with hormone refractory prostatic cancer about one third of the lesions also took up 111In octreotide (7). Even though the uptake was not as great as was seen with carcinoid, this still might be sufficient as a basis for consideration for selecting patients who may be amenable to treatment, especially in those patients with very good uptake. These findings say something interesting about the biology of prostate cancer, that it is a very diverse tumor, with considerable endocrine features that were not previously emphasized, and that somatostatin receptor expression is common. Under the right circumstances, otherwise refractory tumors may respond to octreotide, and, furthermore, this result may be predictable, based on 111In octreotide scanning.

Summary

Definite progress in clinical RAID methods were reported at the Princeton Symposium. Pivotal trial results were reported for Immuno-4-labeled with 99mTc that tend to confirm the earlier promise of this radiopharmaceutical for colorectal cancer assessment. The agent has proven to be better than CT, with respect to determining "resectability" of recurrent colorectal cancer. Furthermore, an antibody imaging method for lymphoma appears to be more useful than standard staging methods for the most difficult diagnostic problems in lymphoma staging, namely, the low-grade lymphomas. Prospects for near-term and long-term advances are bright. In regard to funding agencies supporting oncological applications, a more balanced program is indicated so that advances in therapeutics, basic science, and diagnostic medicine can combine to give the greatest benefits to patients. In this way new therapies will be more optimally used, and basic approaches will be more rapidly applied to important patient problems.

References

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