Principles of Chemoradiation: Theoretical and Practical Considerations

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Chemotherapy agents known to enhance the effects of radiation in preclinical studies have been used concurrently with radiotherapy in numerous clinical trials with the prospect of further enhancing radiation-induced

Introduction

Despite advances and refinements in cancer treatment and an emphasis toward early detection, the vast majority of human malignancies are not effectively treated. Knowledge of the complex nature of human cancer is increasing exponentially as modern molecular biology and genetics reveal potential targets to combat and perhaps some day prevent this dreadful disease. Yet, there is still a need to fully develop and optimize combined-modality cancer treatment to help patients who will not have the opportunity to benefit from the molecular biology revolution.

The combined use of radiation therapy and chemotherapy in cancer treatment is a logical and reasonable approach that has already proven beneficial for several malignancies. Local control of the primary tumor mass (which can often be achieved by high-dose radiation), combined with systemic chemotherapy to control metastatic disease, should provide effective means to combat such a highly complex disease. Moreover, the finding that many chemotherapy drugs enhance the effects of radiation provides even more impetus to integrate both modalities.

The genesis of concurrent chemoradiation dates back to the 1950s when investigators began searching for chemical agents that might enhance the effects of radiation.[1,2] In 1958, Heidelberger et al obtained [potentiation of activity] by combining fluorouracil with radiation in a preclinical study.[3] They treated transplanted murine tumors with fluorouracil 20 mg/kg/day for 7 days and radiation doses of either 15 or 20 Gy. These pioneering studies were later translated into clinical trials, often with contradictory results, such as those observed in the treatment of lung cancer.[4,5] However, a major breakthrough was achieved in the early 1970s when, encouraged by the results obtained with chemoradiotherapy at the Mayo Clinic on gastrointestinal cancers,[6,7] Nigro and colleagues used a combination of fluorouracil and mitomycin concurrent with radiation as neoadjuvant treatment in patients with cancer of the anal canal. They reported that three of three patients achieved complete responses.[8] In two of the three patients, an abdominoperineal resection was performed 2 months after treatment. Histological examination of tissue specimens confirmed a pathologic complete response. The other patient refused surgery but was alive and clinically free of disease 14 months after the treatment. Even though the study included only a small number of patients, the results of this initial pilot study (and subsequent clinical trials) were so dramatic, they prompted a paradigm shift in the thinking of oncologists away from exonerative surgery for anal cancer. Since the 1970s, numerous chemoradiation trials have been performed with differing levels of success in a variety of cancer histologies.

It is most reasonable to ponder why chemoradiation is so successful in the treatment of one cancer histology and yet only provides varying levels of success in others. Furthermore, it is also reasonable to explore the limitations of chemoradiation. The major limitation of combining two modalities has been cumulative normal-tissue toxicity. Either modality when used alone may cause major normal-tissue toxicity, which in some instances can be life threatening. The onset of normal-tissue toxicity limits the dose achievable by either modality alone and thus compromises the administration of the drug or radiation dose. Most experimental models and a number of clinical trials using combined drugs and radiation simultaneously show that normal-tissue toxicity may be enhanced even further.[9,10] Thus, a major barrier in the use of radiation or chemotherapy to treat cancer either alone or in combination is lack of specificity.

A photon beam, no matter how well shaped or conformed to the dimensions of the tumor, will
undoubtedly irradiate some normal tissue. The radiosensitivities of tumor and normal tissues are often similar, or, unfortunately in some cases, the tumor cells may be more resistant than surrounding normal tissues. Radiation alone can and does damage normal tissue if threshold doses are exceeded. Systemic drug therapy theoretically exposes all tissues, normal and tumor alike, to cytotoxic action. Often, normal-tissue toxicity exceeds tumor cytotoxicity, or effective tumor-cell cytotoxicity is compromised by reducing the dose to reduce normal-tissue toxicity to an acceptable level. During chemotherapy, patients frequently relapse after initial treatment and become progressively less responsive to second- or third-line treatments.[11] Combined-modality therapies complicate these issues further. These are the harsh realities of combined-modality therapy that must be dealt with if cancer treatment is to improve using multimodality approaches. Rational and systematic cooperation on the part of basic scientists and clinicians offers the possibility to forge treatment approaches that work. This article will focus on several aspects of combined-modality therapy that should be considered. Space does not permit the review of each radiation–dose-modifying agent in current use; however, the reader is directed to several fine reviews that provide more detail, particularly with respect to specific drugs and radiosensitization.[12-14]

The "Ideal" Radiation Modifier

When considering using the combination of a chemotherapy drug(s) (or radiation-modifying agent[s]) with radiation, it is important to understand the mechanism(s) of action of each modality, how these mechanisms might overlap to enhance one or the other, and how to effectively "time" each agent to yield maximum benefit. It is perhaps worth asking the question, "If one could design an ideal radiation modifier, what would be its characteristics?" Table 1 highlights the characteristics of an "ideal" radiation modifier. Consideration of an "ideal" modifier may be a lofty aspiration, yet it nonetheless provides a standard for which to aim. In principle, the ideal radiation modifier portrayed in Table 1 allows for more radiation dose to be delivered to the tumor (in the case of a protector) and more "effective dose" (in the case of a sensitizer). Most experimental tumors and most human primary tumors respond to radiation treatment in a dose-dependent manner with respect to response and cure. The more dose delivered to the tumor, the greater the likelihood of tumor cure. Likewise, an "ideal" radiation sensitizer has effective antitumor activity against metastatic disease, a major determinant of long-term, disease-free survival. In reality, an "ideal" radiation modifier does not yet exist, but we can use the characteristics of an ideal radiation modifier as a standard as new chemoradiation agents become available.

Radiation Sensitizers

The major reason to consider the use of a radiation sensitizer is to improve local control of disease. A radiosensitizer may not have a direct anticancer effect (as is the case for some hypoxic cell radiosensitizers), or it may be one of a variety of anticancer drugs that, in addition to radiosensitization, exhibits antitumor effects alone. Understanding the mechanism of action of a specific radiosensitizer can affect the way it is used in the clinic. In general, the mechanism by which agents sensitize cells to radiation can be categorized into three broad areas, as discussed below.

Increase in Initial Damage

Radiation-induced cellular effects result from the production of free radical species and/or direct ionization of target molecules. The exact identification of critical cellular structures or molecules and the specific type of damage rendered by radiation are not completely known. However, considerable evidence points to DNA as the critical target for radiation damage,[15] with double-strand DNA breaks as the lethal lesion.[16] Cells die following radiation treatment by mitotic-linked death and/or programmed cell death (apoptosis). An agent that causes more initial damage to critical cellular targets would be expected to enhance the cytotoxic effects of radiation if repair systems become saturated. Halogenated pyrimidines, which in part enhance the radiation response by increasing damage, have been used in chemoradiation studies. Incorporation of halogenated pyrimidines into cellular DNA has been shown to increase DNA damage,[17] as well as compromise repair systems[18], as discussed below.

Repair Inhibition

The ability to repair radiation damage is a vital and necessary cellular function. Repairs in this context "fix" or "undo" the damage to a structure or molecule that is necessary for viability and function. There are several likely ways cells could accomplish this objective. First, molecules that
Chemically restore damaged molecules may be present in cells. An example might be a reducing species that could donate electrons to oxidized (damaged) substrates. Second, there might be a variety of enzymatic systems that can recognize and repair damaged substrates through a set of complex, ordered reactions. Finally, in a very loose sense regarding repair, there may be cellular systems that prevent damage before it occurs. Such systems would involve detoxification of toxic species by either chemical or enzymatic means. Much is being learned about the specific enzyme(s) responsible for the repair of radiation damage; undoubtedly in the future, specifically targeting these enzymes will afford another avenue for chemoradiation studies.

The radiation dose-response curve for most human tumor cell lines derived from solid tumors is characterized by a shoulder in the low-dose region of the curve. The implication of the shoulder region of the curve is that cells have the capacity to repair radiation damage, particularly for radiation doses delivered in radiotherapy (~2 Gy). Extensive studies reveal that the time required for maximal radiation damage repair varies between 3 and 6 hours. The extent of repair is dependent on the particular cell type and can be quite significant, particularly in tumors that do not respond well to radiation, such as melanoma and glioblastoma. Normal tissues can also repair radiation damage to different extents. Time-dependent repair of normal tissue is the major reason why radiation dose is fractionated. Thus, cells of tissue treated with 2 Gy on Monday morning will have repaired all of the damage they are capable of repairing by the time the next fraction is given on Tuesday, and so forth. Ideally, agents that inhibit radiation damage repair (in the tumor) need to be present daily as radiation is administered. Because of the lack of specificity of most agents currently used, normal tissue may also be radiosensitized.

Cell-Cycle Redistribution

Tumor growth is governed by (1) the fraction of cells within the tumor that are actively dividing (cycling vs quiescent cells); (2) the duration of the cell cycle; and (3) the cell-loss factor. It has been known for more than 30 years that cells vary in their response to radiation as a function of their position in the cell cycle; cells in G2/M at the time of irradiation are approximately threefold more sensitive than cells in late S-phase/early G1. The exact reason(s) for the variation in sensitivity to ionizing radiation throughout the cell cycle is not known. An agent that selectively blocks tumor cells in a radiosensitive phase might provide a means for significant radiosensitization.

Many chemotherapeutic agents are capable of imposing cell-cycle blocks with subsequent radiosensitization. For example, preclinical studies have shown that paclitaxel (Taxol), a drug currently being evaluated in clinical chemoradiation trials, imposes a significant G2/M block and radiosensitizes many human tumor cell lines and murine tumor models. Figure 1 demonstrates the dependency of the G2/M block for radiosensitization of MCF7 breast cancer cells. Note that radiosensitization did not occur until cells were emptied from S phase into G2/M. Armed with encouraging preclinical results, a number of institutions are evaluating the combination of paclitaxel and radiation in a variety of tumor types. Will the preclinical information and enthusiasm be translated into benefits for cancer patients? The answer to this question must await the results of the trials. However, are the studies combining paclitaxel and radiation designed properly for success, and perhaps with equal importance, if the trials fail will we know why? These are difficult questions to answer.

Clinical trials are traditionally launched assuming that the results and possibly the mechanisms observed using laboratory in vitro and in vivo models will translate into the human model. This is a minimal assumption. Sadly, few clinical studies are designed to actually determine whether or not expected mechanisms are operational in the human model. Preclinical studies showed that for paclitaxel to radiosensitize, cells need to be moving in the cell cycle in order to block in G2/M. Cells in plateau phase (G0) are not radiosensitized by paclitaxel. Therefore, tumors with a low growth fraction (few cells cycling) would not be expected to be radiosensitized to the extent of tumors with high growth fractions. Considerable data are available regarding the growth kinetics of human tumors; thus, phase II trials should initially be undertaken to treat those tumors that have the best chance to respond.

Dose Effect Factor/Therapeutic Gain

In order for an agent to be considered for use in chemoradiation, preclinical studies are usually conducted. Radiation dose-response curves are generated for a variety of tumor cell types in the absence and presence of the drug. Depending on what is known about the drug’s mechanism of action, various concentrations and durations of exposure either before, during, or after radiation treatment are examined. After the cytotoxicity of the drug treatment alone is normalized, the effect
of the drug on radiosensitivity can be assessed for a given end point. In the case of cell-survival curves, the dose-effect factor is calculated at a given survival level. The dose of radiation alone required to yield a given survival level is divided by the dose to yield the same survival level for the radiation/drug combination. If the ratio yields a number > 1, the agent [enhances] the radiation response; likewise, if the agent yields a ratio < 1, the agent [protects]. Dose-effect factors may be determined not only for cells in culture, but also for tumor and normal tissues in animal models.[14] Determining dose-effect factors in animal models provides the option of determining the therapeutic gain, which is calculated by dividing the dose-effect factor of the tumor by the dose-effect factor of the normal tissues. In order for chemoradiation to be successful, a therapeutic gain > 1 is the goal. In reality, however, determination of a meaningful therapeutic gain in experimental models is both laborious and difficult to interpret. It is laborious in the sense that combined chemoradiation studies in animals are time consuming, costly, and may involve numerous permutations of drug concentrations and timings. It is difficult to interpret because most rodent tumor models with their rapid growth kinetics are not thought to be reflective of human tumors. Human tumor xenografts in immune-compromised mice are an alternative to rodent tumors; however, these are human tumors growing under the control of the mouse physiology. On the other hand, the radiation response of normal tissues in mice closely matches the response seen in humans,[14] and may provide the clinician some idea of which and to what extent normal tissues are vulnerable. Because of the issues discussed above, new agents are frequently brought to chemoradiation clinical trials without preclinical therapeutic gain information. Commonly, dose-effect factors are determined for cell lines (human tumor), and perhaps a few studies are conducted in mice regarding efficacy of tumor response with combination therapy. Rarely are murine normal-tissue dose-effect factors determined. It may be rationalized that most new agents considered for chemoradiation have already undergone clinical trials as single agents and much is already known about their toxicity profiles. What is not known, however, is the extent that radiation will enhance these toxicities. Given these realities, what dose-effect factor value (derived primarily from in vitro studies) warrants the introduction of a new agent to chemoradiation evaluation (ie, 1.1, 1.5, 2.0, or higher)? This question is indeed difficult to answer. A dose-effect factor of 1.1 means that a radiation dose will be enhanced by 10%, a seemingly modest amount. However, if one assumes that the radiation response will be enhanced by the agent for each radiation fraction, over the course of 30 fractions this could amount to a significant enhancement, even for a dose-effect factor of 1.1. Of course, there are qualifiers. For example, the inherent radiosensitivity of the tumor cells may greatly influence the net response of an agent that yields a dose-effect factor of 1.1. Figure 2 is a theoretical plot of the number of 2-Gy fractions required (out of a normal 30-fraction course) to obtain a 90% tumor cure as a function of the dose-effect factor for three different initial surviving fractions at 2Gy (SF2Gy) (0.5, 0.6, 0.7). A number of assumptions are made when generating this plot, including (1) a 1-g tumor (1-cm diameter, 10⁶ cells); (2) a 90% tumor cure, a probability that requires a total radiation dose to reduce survival to < 1 × 10⁻⁹; (3) no repopulation during treatment; (4) a completely aerobic tumor; (5) SF2Gy determined using the α/β model, with an α/β ratio = 10; (6) uniform radiosensitivity for all cells in the tumor; and (7) complete radiation repair for each fraction. Enhancement is calculated by multiplying the effective dose per fraction by the dose-effect factor. As apparent from Figure 2, the inherent radiosensitivity of the cells within the tumor is a major determinant of the ability of an agent to reduce the number of fractions required for a 90% cure. For relatively sensitive tumors (SF2Gy ≤ 0.5), dose-effect factors in the range of 1.2 to 1.5 can be effective if the modifier is given roughly 30% to 70% of the total number of fractions. Whereas, for less sensitive tumors (SF2Gy > 0.6), the modifier should have a dose-effect factor in excess of 1.9 if any effect at the 90% tumor-cure level is to be realized. Whether a tumor dose-effect factor of 1.1 for a particular agent can be achieved in the clinic depends on numerous factors.

**Potential Barriers to the Effective Use of Chemoradiation Normal-Tissue Toxicity**

As discussed above, increased radiation-induced normal-tissue toxicity due to chemotherapy agents administered concurrently is a major problem. Use of three-dimensional treatment planning and conformational delivery of the radiation beam to the tumor to minimize dose to normal tissues hold some promise of further enhancing the effectiveness of chemoradiation. Theoretically, use of radiation protectors should also be a beneficial addition to a chemoradiation protocol.
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The question to ask is: Does the drug actually get to the tumor cells an adequate enough concentration to (1) kill the tumor cell, or (2) in the case of chemoradiation, enhance the radiation response? While this is a rational and reasonable question, few studies have been conducted to obtain the answer because the task is quite difficult. Taking multiple tumor biopsies is inconvenient, adds cost to the study, and can pose certain risks to the patient. The location of the tumor for biopsies is often problematic, as is the concern of multiple biopsies in an irradiated field. The interpretation of drug concentration in tumor biopsies can be complicated because of the infiltration of host cells into the tumor mass, as discussed below. Lastly, the availability of suitable assays for the drug and its metabolites is not always straightforward. These concerns can be partially addressed for agents whose mechanisms of action are known, because in this setting, functional biological assays can be conducted. For example, paclitaxel treatment results in a G2/M arrest in cells in culture. If arrest of cells in G2/M is required for paclitaxel-mediated enhancement of radiation toxicity, then determining cell-cycle parameters from biopsy material taken from the patient's tumor as a function of time after paclitaxel administration should reveal whether the drug is reaching the tumor cells in concentration.
that is adequate enough to achieve the goal.
In a National Cancer Institute pilot clinical trial evaluating continuous-infusion paclitaxel with
concomitant radiation therapy for head and neck cancer, tumor biopsies were taken prior to and 48
to 96 hours after paclitaxel infusion. The tumor samples were analyzed by flow cytometry (Figure 3).
Seven of nine patients showed no cell-cycle blocks as a result of the 48- to 96-hour continuous
infusion of paclitaxel (started at 105 mg/m² to 120 mg/m²). Figures 3A and 3B show pre-paclitaxel
and post-paclitaxel treatment DNA flow-cytometry profiles from a patient’s tumor that did not show
a treatment-related cell-cycle block in G2/M. One patient’s tumor did show some modest cell-cycle
redistribution as a result of the paclitaxel treatment (Figures 3C and 3D).
The reason(s) for the failure of paclitaxel in this study to arrest cells in G2/M are most likely multiple.
First, the concentration of paclitaxel infused may not have been adequate. Second, should drug
resistant phenotypes be present or result from the continuous paclitaxel treatment, one would not
expect to see cell-cycle redistribution. Third, the biopsy taken represents only a small fraction of the
total tumor mass; perhaps, the biopsies were taken from areas where cells were quiescent and not
cycling. Fourth, 48 to 96 hours of continuous drug infusion may not be long enough to detect
significant changes in cell-cycle distribution. Lastly, currently unidentified factors could contribute to
the lack of the G2/M arrest. This example highlights the complexity of asking the simple question of
whether or not a drug reaches and affects a tumor; nonetheless, attempts should be made to obtain
this type of important information. If a drug fails to be an effective radiation modifier, it is important
to know why.

Knowledge of Optimal Timing of Agents
Preclinical in vitro studies can contribute considerable information toward defining the optimal timing
of a drug and radiation in clinical protocols. In fact, timing considerations in chemoradiation clinical
protocols are often based, in part, on scheduling data derived from preclinical in vitro studies. There
can, however, be a vast difference between controlled in vitro studies and the in vivo situation.
Most in vitro chemoradiation studies are conducted with a single radiation dose with drug treatment
occurring before, during, or after radiation treatment. Radiation is delivered by daily fractions (often
twice per day). However, if the drug is administered as a weekly bolus, will sufficient concentrations
of the drug be present to enhance the radiation doses that are administered by the end of the week?
Moreover, will the radiation doses given the first week affect the ability of the drug given in
subsequent treatment weeks to enhance radiation effects? In the case of cell-cycle specific drugs,
does radiation treatment (which alone can induce cell-cycle blocks) retard the ability of the drug to
influence the cell-cycle distribution? For example, numerous investigators have shown that paclitaxel
given before radiation results in radiation enhancement of cytotoxicity.[26,27] However, treating
cells first with radiation has been shown to antagonize the cytotoxic effects of paclitaxel.[41] One
wonders if this is an issue in the present clinical protocols combining paclitaxel and radiation.
Considerable data exist for certain tumor types suggesting that after the first 3 to 4 weeks of
fractionated radiotherapy, the surviving tumor cell clonogens have an increased growth rate.[42] To
compensate for this accelerated tumor cell growth/repopulation, additional radiation doses would be
required if the radiation course is protracted beyond the scheduled time. For oropharyngeal tumors,
it is estimated that an additional 0.6 Gy/day would have to be added to compensate for
repopulation.[42] If true, the use of cell-cycle-specific radiation enhancement agents might be more
effective if given at the end of the normally scheduled radiation protocol rather than at the
beginning. Similarly, it might be interesting and efficacious to use halogenated pyrimidines toward
the end of radiation treatment when tumor cell growth is accelerated. The downside of this approach
is that radiation treatment may stimulate the repopulation of certain normal tissues.
It is not entirely obvious exactly how the issue of timing should be approached in clinical trials. This
is why it is important to know the mechanism of action of an agent brought into clinical trials and
how the agent interacts with radiation, at least at the cellular level. With this information, one could
biopsy tumor material during the trial to determine if the basic mechanisms presumed to be
operational are indeed working in the patient’s tumor. If not working, alternate timing protocols
should be considered.

Physiologic Considerations
A variety of physiologic factors, some unique only to the tumor, can influence a tumor’s response to
drugs and radiation. Such factors include tumor blood flow,[37] oxygen transport,[43] hypoxia,[44]
interstitial fluid pressure,[36,45] and tumor pH.[46] In radiobiology, significant research has gone
into determining the impact of hypoxia on the radiation response. The existence of hypoxic regions
in human tumors was hypothesized in the mid 1950s,[44] and over the past several years, the
presence of hypoxic regions in human tumors has been verified by oxygen electrode studies.[47]
The importance of hypoxic regions (both chronic and acute) in tumors to oncology is that (1) hypoxic cells can be viable and capable of proliferation if oxygen becomes available; (2) hypoxic cells are approximately threefold more resistant to radiation than aerobic cells and (3) the presence of hypoxic cells in a tumor is an unfavorable prognostic indicator for local control of tumors treated with either radiotherapy or surgery.[47] In the context of chemoradiation, the presence of hypoxic regions in tumors could mean that drug delivery to these areas is compromised. If oxygen cannot readily reach these areas, a low molecular-weight drug is also unlikely to reach the areas. Research is ongoing to identify a means of increasing oxygen levels to hypoxic regions,[48] and to develop new sensitizers or cytotoxins of hypoxic cells.[49,50]

**Drug Resistance**

The development of drug resistance during the course of chemotherapy is a formidable problem. While much has been learned about the cellular/molecular mechanisms of drug resistance, approaches to circumvent this problem have yet to be identified. Drug resistance in tumor cells might effectively decrease the dose of drug available for radiosensitization. Several studies have convincingly shown that drug-resistant cells are not radioresistant;[51] however, to our knowledge, no information exists as to whether drug-resistant cells can be radiosensitized by the drug(s) to which they are resistant. Stated differently, it is not known if a cell’s mechanism for detoxication of cytotoxicity results in loss of radiosensitization.

**Host-Cell Infiltration of Tumor**

As early as 1863, tumor infiltration by leukocytes was noted, and based on this observation, Virchow concluded that tumors arise in areas of chronic inflammation.[52] More recently, the presence of leukocytes has been linked to the idea of ‘immune surveillance,’ which proposed that tumor cells are recognized as antigenically different from normal host cells and thus incite an immune reaction.[53] In their reports, pathologists seldom mention the presence of reactive cellular infiltration.[54] In an analysis of breast carcinoma, Underwood found that the mean total tumor-cell volume of two medullary carcinomas was 64.5%, while in ten scirrhous carcinomas, the tumor-cell volume was only 21.5%.[55] Thus, it is possible that a significant portion of the tumor-cell mass may be composed of cells other than malignant cells.

We have evaluated the extent of tumor infiltration by normal host leukocytes from biopsies of 26 human tumors from the lung, including both primary and metastatic lesions. Delineation of leukocyte infiltration was accomplished by double-staining tumor sections with a pan antileukocyte monoclonal antibody (HLE-1) and propidium iodide. Images of the staining patterns of both the total nuclei (stained by propidium iodide) and leukocytes (labeled with a biotinylated anti-mouse secondary antibody and FITC-streptavidin) examined under low magnification were acquired and stored using a laser scanning microscope and computer-based image analysis system. The staining pattern of individual leukocytes varied markedly throughout all tumor sections examined. In general, the leukocytes were seen in either clumps of varying sizes or as individual leukocytes scattered throughout the entire tumor section. Representative samples are shown in Figure 4. The pattern in Figure 4A containing a moderate infiltration of leukocytes is representative of many specimens analyzed, while in Figure 4B, the leukocytes appear randomly distributed throughout the section. Figure 4C shows an island of cells surrounded by leukocytes in a section having a high degree of leukocyte infiltration. The percentage of tumor leukocyte infiltration was quantitated by taking the ratio of leukocyte staining to the nuclei staining for each section. The proportion of leukocytes in the individual tumors ranged from 4% to 90%, with a mean of 40% (Figure 5). In 15 of 26 specimens, the leukocyte fraction was equal to or greater than 40% of the entire tumor sample. In addition, we also attempted to classify the types of leukocytes present in 15 of 26 patients using antibodies specific for monocytes/macrophages, granulocytes, T-cell lymphocytes, and B-cell lymphocytes. A majority of the analyzed specimens contained both macrophages and granulocytes (12 of 15 samples), while only two samples had T cells in excess of 19%.

The reason(s) for the extensive infiltration of host cells in these tumor samples and whether their presence poses a barrier to effective chemoradiation (or chemotherapy alone) is not known. Without doubt, the presence of these cells within a tumor biopsy complicates precise determination of tumor-cell drug uptake and functional cellular/molecular assays specific to drug treatment. Are these cells activated/inactivated for tumoricidal activity? Do these cells represent a means of drug detoxification that would in effect decrease the drug concentration delivered ultimately to tumor cells? Does the response of these hematopoietic cells to various treatment protocols have important influences on what is perceived as a partial or complete tumor response to cytotoxic therapies? The answers to these questions require additional confirmation and an understanding of their importance.

**Figure 4**

The pattern in Figure 4A containing a moderate infiltration of leukocytes is representative of many specimens analyzed, while in Figure 4B, the leukocytes appear randomly distributed throughout the section. Figure 4C shows an island of cells surrounded by leukocytes in a section having a high degree of leukocyte infiltration. The percentage of tumor leukocyte infiltration was quantitated by taking the ratio of leukocyte staining to the nuclei staining for each section. The proportion of leukocytes in the individual tumors ranged from 4% to 90%, with a mean of 40% (Figure 5). In 15 of 26 specimens, the leukocyte fraction was equal to or greater than 40% of the entire tumor sample. In addition, we also attempted to classify the types of leukocytes present in 15 of 26 patients using antibodies specific for monocytes/macrophages, granulocytes, T-cell lymphocytes, and B-cell lymphocytes. A majority of the analyzed specimens contained both macrophages and granulocytes (12 of 15 samples), while only two samples had T cells in excess of 19%.

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Conclusions

This review has posed more questions than answers. The combined use of radiation modifiers to effectively enhance the radiation response is indeed complex. It must be understood that despite the myriad problems and concerns regarding concurrent chemoradiation, under certain circumstances, the approach works in that better local control can be achieved with acceptable normal tissue toxicity. Chemoradiation trials can be designed not only to study possible efficacy for the cancer patient, but to gain more information regarding the mechanisms of action (in the patient) and the pharmacokinetics/pharmacodynamics of drug uptake and action in the tumor/tumor cell. Based on concepts brought forth in this review, Table 2 lists several possible considerations for chemoradiation trials. While it is realized that designing clinical trials to address specific basic science questions is a more difficult task than is encountered in the research laboratory, to not do so consigns the trial to empirical permutations. There is nothing particularly wrong with empirical approaches; however, teamwork between basic scientists and clinicians can add a new dimension of scientific information that will undoubtedly advance the area. For example, if the drug(s) is not reaching the target in the patient’s tumor in sufficient concentrations to enhance the radiation response, research needs to focus on a means of enhancing drug delivery.

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