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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

FDA REQUIREMENTS FOR APPROVAL OF DRUGS TO TREAT NON-SMALL CELL LUNG CANCER

This is one of several reports concerning disease-specific requirements for new drug approval. This report deals specifically with non-small cell lung cancer (NSCLC) and issues concerning the efficacy endpoints that would be critical to FDA evaluation and approval of new drugs in the treatment of this disease. The recommendations in this report should be applied to the design of drug development Phases II and III in NSCLC. This subject was discussed at the Oncologic Drugs Advisory Committee (ODAC) meeting on February 1, 1990. At this meeting, Dr. Daniel C. Ihde presented a very comprehensive review of NSCLC, including the natural history of this disease and results of selected clinical trials. Dr. Ihde is Professor of Medicine at the Uniformed Services University in Bethesda and maintains an international reputation as an authority in the treatment of lung cancer. Dr. Ihde's lecture and the discussion at the ODAC meeting as well as various literature sources contributed to the content and conclusions presented in this report. It is important to note that there was general agreement among the committee members on most, if not all, of the issues presented for their discussion and recommendation. In this report, the role of chemotherapy in a variety of treatment settings (eg. metastatic disease vs. adjuvant or neoadjuvant) will be evaluated. The results of previous clinical studies will be the basis for predicting those endpoints which would be most valuable in evaluating the relative efficacy of an anticancer drug or drug regimen. The potential for various end-points to serve as surrogates for survival and/or quality of life will also be evaluated.

BACKGROUND INFORMATION

Incidence and Prognosis

Lung cancer continues to be a major health hazard in the U.S. and is the most common cause of cancer death in this country. According to American Cancer Society predictions, NSCLC will account for approximately 110,000-120,000 deaths this year alone. About two-thirds of NSCLC patients present with disease that is beyond "curative" surgical resection. The estimated 5-year survival is 8% for patients who have disease that is regionally advanced and <1% for those who present with distant metastases. The survival is also extremely poor for the approximately 50% of patients who relapse following initial surgical resection of localized NSCLC. Therefore, improvement in the survival of the majority of patients with NSCLC requires the development of more effective chemotherapeutic drugs or other systemic therapies which are effective against covert and overt

distant metastatic disease.

Single Agent Chemotherapy

Although, chemotherapy has been shown be effective in the treatment of small cell undifferentiated carcinoma of the lung (SCLC), the role of chemotherapy in the management of NSCLC has not been established. Currently approved drugs, when used as single agents, have objective response rates in NSCLC of ≤25%. All controlled clinical studies reported prior to 1980 showed that chemotherapy does not improve survival significantly in patients with metastatic disease or when given as an adjuvant following local resection or radiotherapy. More recently, combination regimens, most of which have included cisplatin, have yielded higher remission rates, and there is evidence to suggest that for the first time complete responses may occur. In uncontrolled studies, it is difficult to know whether the higher response rates in more recent studies are due to better drug activity or the inclusion of more patients with less advanced disease or other favorable prognostic characteristics.

Combination Chemotherapy

A review by Kris and Gralla of experience in treating 1604 patients with NSCLC, indicated that the response rates to cisplatin-containing combination programs range from 29-49%. The combinations consisting of vindesine plus cisplatin and mitomycin-C plus a vinca alkaloid plus cisplatin appeared to be particularly active with objective response rates of 35% and 49%, respectively. In single institutional studies, responses in some of the patients treated with these regimens were very durable. Vindesine plus cisplatin given at MSKCC resulted in a CR rate of 8.5%. In the subgroup of 23 patients who achieved a CR, the median duration of response was 18 months (range, 10-48) and median survival was 29 months (range, 12-48+). The fact that isolated CNS relapse occurred in 6 of 20 patients evaluable for this complication, provides important information concerning the natural history of this disease which may need to be considered and addressed when more effective systemic treatments become available.

Whether cisplatin containing-regimens improve the overall survival of patients with NSCLC is not certain. An ECOG study comparing 3 different cisplatin-containing regimens with CAMP (cyclophosphamide, adriamycin, methotrexate, and procarbazine) showed no difference in the median survivals (23-25 weeks) even though the cisplatin-containing regimens tended to have higher response rates than that (16%) achieved with CAMP. Also, the median survival of these patients was not much different from a historical group of good performance status extensive stage patients (VA Lung Group) who were treated with supportive care alone (18-20 weeks).

In summary, combination chemotherapy (particularly cisplatin-containing regimens) in NSCLC appears to result in higher response rates than single-agent therapy. Responding patients appear to live longer than non-responders but the data do not convincingly prove that responders live longer than patients with stable disease. Overall survival is almost certainly not improved by single-agent therapy. Overall survival is possibly improved by combination chemotherapy but the data from uncontrolled studies have not been conclusive in this regard. To adequately evaluate the effect of investigational combination chemotherapy on survival it is probably necessary to follow the approach of several recent studies that included randomized control arms consisting of a best supportive care (BSC) arm not receiving chemotherapy.

There are several published reports of randomized controlled trials in NSCLC comparing combination chemotherapy with BSC. Only one of these studies demonstrated a statistically significant increase in survival with chemotherapy (Rapp E et al. J Clin Oncol 6:633-641, 1988). This was a multi-institutional Canadian study which randomized patients (Mountain stage III or IV) to receive chemotherapy with vindesine plus cisplatin (VP) (44 pts), cyclophosphamide, doxorubicin, plus cisplatin (CAP) (43 pts), or BSC (50 pts). The median survival was 32.6 weeks in the VP group ($p = 0.01$) and 24.7 weeks in the CAP group ($p = 0.051$) compared to 17 weeks in the BSC group. Certainly, the extension in survival by 2-4 months by chemotherapy must be weighed against the potential toxicities and palliative effects of treatment, particularly since chemotherapy in these patients is not curative. The value of such a modest survival benefit is open to controversy and many investigators would still argue in favor of the use of a BSC arm until the overall benefits of chemotherapy become more evident. Such a controversy also argues in favor of employing quality of life assessments in the evaluation of drugs for approval. In other similar randomized studies, there is a tendency for the chemotherapy group(s) to have a slightly longer survival than BSC but the results are not statistically significant, possibly due to the lack of statistical power in relatively small individual studies to detect a slight survival advantage attributable to chemotherapy. Thus, it is difficult to draw firm conclusions from the single more promising Canadian study at present.

Relationship Between Stage and Survival

Before evaluating the criteria for drug approval in NSCLC, pertinent information regarding staging and survival will be briefly reviewed. Patients with clinical stage I and II (Mountain CF. Chest 89:225-233, 1986) should undergo surgical resection, if at all possible, since this procedure is potentially curative in as many as 45% and 25%, respectively. Surgery may also cure a small proportion (15%) of patients with stage IIIa disease but the median survival of all stage IIIa

patients is only 12 months. The median survival of patients with disease that is advanced beyond any chance for surgical resection is even shorter (8 months for stage IIIb and 4 months for stage IV), and long-term survival for these patients is much less than 5%. It is apparent from these survival statistics that if survival is used as an end-point it would not take an inordinate amount of time (median follow-up of one year or less) to estimate the effect of an investigational agent on the outcome of patients with stage III-IV NSCLC. Evaluation of chemotherapy in earlier stage (I or II) patients used as an adjuvant to local treatment will require somewhat longer periods of follow-up.

Adjuvant and Neoadjuvant Chemotherapy

In addition to its use in patients with metastatic disease, chemotherapy for NSCLC is also being investigated in patients with disease that is localized or locally advanced. In some studies, adjuvant chemotherapy is administered shortly after surgical resection (with or without local radiation) in hopes of reducing the chance of local and systemic recurrence and to improve long-term survival. In other studies, chemotherapy is administered prior to local/regional treatment with surgical resection or irradiation. In this setting, so-called "neoadjuvant" chemotherapy has the additional potential of enabling surgical resection to be performed in otherwise unresectable patients (the ultimate significance of which remains to be determined). Patients who are eligible for these studies are those who have no evidence of distant metastatic disease but the extent of locoregional disease may vary. Patients with stage IIIa or IIIb may be eligible for such protocols. Stage IIIa is regionally advanced but may be potentially resectable. Stage IIIb is more regionally advanced than IIIa but all the disease may still be encompassed within a "curative" radiation port. In contrast to adjuvant studies, neoadjuvant studies have the potential for evaluating chemotherapy response rates (including pathological complete responses) as well as survival.

The only results of neoadjuvant chemotherapy that are available are from uncontrolled studies. There is considerable variability in the results, probably because the studies differ in regards to patient entry criteria, the specific drugs given, and the use of local radiotherapy in addition to chemotherapy in some trials. The incidence of resectability following chemotherapy varies from 14% to 88% and median survival ranges from 9 to 32 months indicating that patients with markedly disparate tumor burdens were entered on different trials. The preliminary results of one neoadjuvant study appear to be encouraging. Gralla and Martini at MSKCC gave neoadjuvant mitomycin-C plus vinblastine or vindesine plus cisplatin (2-3 courses) to patients with clinically apparent involvement of the mediastinal lymph nodes (N2). Chemotherapy resulted in a 73% remission rate including 17% complete responses. It is apparent from this and other studies administering chemotherapy without

subsequent surgery that response rates to chemotherapy in patients with disease limited to the chest are higher than for patients with more widely disseminated disease. A similar relationship has been found in other neoadjuvant studies, but some of these enhanced response rates could be attributed to local radiation therapy. In the MSKCC study, fifty-one percent of the patients were able to undergo complete resection; 38% of 21 evaluated pathological specimens were negative for tumor. The three-year survival is estimated to be 34%. These results appear markedly improved from the historical experience at that institution with such patients treated previously without neoadjuvant chemotherapy (resection rate of only 14% and 3-year survival rate of only 6%). It should be noted that surgical resection may be technically more difficult following neoadjuvant chemotherapy and/or radiation therapy. Generally, these neoadjuvant studies have shown that patients who are able to undergo complete surgical resection and whose specimen is microscopically free of residual tumor have the best chance of remaining free from local recurrence.

An important characteristic of the MSKCC studies noted above is that both the historical control group and the neoadjuvant patients were staged using the results of chest x-rays and bronchoscopies and not CT scans. This would tend to minimize the possibility of the so-called "Will Rogers effect" accounting for the observed improvement in the results. In other words, the results were not better in the later study compared to historical controls because CT scans were used to exclude patients with otherwise undetectable metastases (and worse prognosis). Certainly this phenomenon must be considered when evaluating the results of trials comparing results to a historical control group. Consideration should also be given to the possibility that uncontrolled neoadjuvant studies select patients who are more likely to tolerate both chemotherapy and surgery; such patients also may be expected to have a relatively better prognosis.

The role of combination chemotherapy as an adjuvant, or neoadjuvant, to locoregional radiation therapy in the treatment of patients with unresectable (locally advanced) NSCLC is not clear. There have been several randomized studies comparing radiation therapy alone with radiation plus chemotherapy, utilizing different drug regimens, only some of which contained cisplatin. Only one study showed a statistically significant difference in survival between the groups. This study was conducted by CALGB and randomized stage III (T3 and/or N2, M0) patients to receive radiation alone (6000 cGy) or radiation following chemotherapy with vinblastine plus cisplatin (Dillman RO et al. N Engl J Med 323:940-945, 1990). Response (including tumor regression as well as PR defined by classical criteria) was observed in 43% of the radiation alone group (77 pts) and 56% of the chemotherapy plus radiation group (78 pts) ($P = 0.092$). The median survival was 13.8 months in the group treated with radiation plus chemotherapy compared to 9.7 months in group

treated with radiation without chemotherapy (P = .0066).

Additional randomized controlled studies are needed to determine the role of chemotherapy as an adjunct to surgery and/or radiation therapy in either operable or locally advanced unresectable NSCLC. These studies should compare surgery and/or radiation therapy alone vs treatment with these local modalities following the administration of the best available combination chemotherapy. In patients with clearly resectable disease, studies should evaluate treatment with surgery alone or surgery followed by adjuvant chemotherapy; in some studies chemotherapy may also be given prior to surgery. The recently proposed SWOG Thoracic Oncology Program is planning a study in patients with stage Ib, II and selected IIIa (T3N0) NSCLC to evaluate the role of chemotherapy since patients will be randomized to undergo surgery alone or surgery preceded and followed by etoposide plus cisplatin chemotherapy. In another proposed SWOG study, patients with stage IIIa and selected stage IIIb disease will be randomized to receive either radiation therapy alone or neoadjuvant chemotherapy followed by radiation and then surgery. The role of chemotherapy will be difficult to determine from the results of the latter study, but controlled trials 20 years ago did not demonstrate benefit from preoperative irradiation in this setting.

Clinical Endpoints

Response rate: There are numerous reports of clinical trials in advanced NSCLC in which patients were randomized to receive different chemotherapeutic agents alone and in combination. Earlier trials involved drugs other than cisplatin. The objective response rates in these studies ranged from 0% to about 30%, depending upon the drug and the particular study; however, there was no meaningful correlation between response rate and survival. More recent studies have included cisplatin-containing combinations in at least one of the treatment arms. The response rates to the cisplatin-containing regimens tend to be higher (4-53%) and in a few of these studies the higher response rate in the cisplatin-containing arm is also associated with a significantly better median survival. However, such a correlation between response rate and survival is not a consistent finding. There are several randomized studies which compare a variety of combinations containing different platinum compounds, and again no meaningful correlation between response rate and survival is apparent. As a matter of fact, there are two studies in which a platinum-containing regimen (mitomycin-C, vinblastine, and cisplatin or MVP) resulted in the best response rate but was associated with the worst survival (Ruckdeschel JC et al. J Clin Oncol 4:14-22, 1986; Bonomi PD et al. J Clin Oncol 7:1602-1613, 1989). In both studies, there were multiple treatment arms containing relatively large numbers of patients. In one of the studies (Bonomi PD et al.), one of the five treatment arms (carboplatin alone) resulted in one of the lowest

response rates (9%) but the longest median survival (7 months vs. 5-6 months).

The above results demonstrate the limitations of the traditional Phase II approach of using response rate as a sole parameter for evaluating the efficacy of chemotherapy in NSCLC probably because responses to current drugs yield only very modest degrees of tumor reduction. If substantial proportions of complete responses result from new chemotherapy programs, it is highly likely that response rates will correlate much better with overall survival.

Response duration and freedom from relapse: The duration of response, which is often used as a measure of a treatment's relative effectiveness, is dependent upon several different tumor-related factors. One of the factors which determines the duration of response is the growth rate of the tumor. Thus, it has been shown that in NSCLC the duration of response can vary with the time it takes to achieve a response (Ruckdeschel JC et al. J Clin Oncol 4:14-22, 1986); eg. the longer it takes to respond, the longer will be the duration of response. Therefore, in uncontrolled clinical trials, duration of response contributes only a limited amount of information in addition to response (particularly, complete response) rate.

Freedom from relapse is an endpoint with some similarities to response duration but can be applied currently only in adjuvant studies in which the patients have undergone surgical resection or obtained complete response to chest irradiation. However, a treatment that prolongs freedom from relapse may not necessarily prolong overall survival. This has been seen with some adjuvant breast cancer studies and two well-known examples of this finding exist in randomized trials of chemotherapy after surgical resection of NSCLC. The value of a treatment that prolongs the disease-free period but not overall survival can be extremely difficult to judge; it may well depend on whether tumor-related symptoms are better palliated in patients on the therapy which improves freedom from relapse. Usually, such a determination cannot be adequately made outside of controlled clinical trials.

Relief of symptoms: Many patients with NSCLC, particularly those with locally advanced or metastatic disease, have disease-related symptoms. Intrathoracic processes such as pleural effusion, superior vena cava syndrome, atelectasis, and endobronchial lesions may cause a variety of symptoms including dyspnea, cough, pain, and hemoptysis. Local radiotherapy is often effective in the palliation of many of these complications. In the case of SCLC, these symptoms may also be effectively improved with chemotherapy. However, there is limited information concerning the effect of chemotherapy on such complications in NSCLC.

A recent study evaluated the effect of EMV (EDAM, mitomycin-C and vinblastine) combination chemotherapy on a variety of symptoms in 85 patients with stage III or IV NSCLC (Kris MG et

al. Proceed ASCO 9:229, 1990). This study utilized a disease specific patient questionnaire, which employs a visual analogue scales (VAS) instrument, to quantitate patients' perceptions relating to cough, dyspnea, pain, hemoptysis, strength, activity, and anxiety. VAS scores, Karnofsky performance status (KPS), and body weight were evaluated before and after EMV chemotherapy. Pretreatment, cough was noted in 71%, dyspnea in 58%, pain in 51%, and hemoptysis in 14%; at least one of these symptoms occurred in 88% of the patients, and two or more occurred in 58%. The median KPS at baseline was 80%. EMV chemotherapy resulted in a response rate of 59% and a median survival (in all patients) of 12.8 months. With the exception of strength, there was significant improvements in each of the VAS-evaluated symptoms. The degree of improvement in three of the symptoms (cough, pain, and hemoptysis) was significantly better for patients who had a response to EMV than for non-responders; the trend was the same in the case of dyspnea but the result was not statistically significant. In addition, 62% of the patients (overall) gained weight and KPS was improved in 44% and maintained in 40%. By measuring the effect of chemotherapy on disease-related symptoms, as well as response rate and survival, the results of studies such as this one present a more meaningful understanding of the efficacy of the treatment under evaluation.

Relative cost: One of the more controversial issues in the evaluation of a treatment, at least one for conventional use, relates to relative cost. There is very little data concerning this matter since the cost of a particular investigational treatment regimen is often not evaluated and difficult to isolate from the routine costs of patient care. Many different costs must be considered in addition to the actual cost of the drug(s) and administration such as the number of days of hospitalization and clinic visits. Also to be considered are the costs of any ancillary studies (eg. laboratory tests and imaging studies) that would be required to monitor for potential toxicities, particularly if such tests are to be part of standard practice (eg. MUGA scans, methotrexate levels). Of course, the cost of the treatment being evaluated must be related to standard modalities and/or to BSC. Relative cost considerations are of major socioeconomic importance but these issues are not currently evaluated by the FDA as part of the drug approval process. If the findings of the randomized Canadian study of chemotherapy versus BSC in NSCLC - that costs were actually higher in the BSC arm because of increased hospitalization - can be confirmed, this issue may merit reconsideration.

Prognostic Factors

Most studies of NSCLC include patients with all major subtypes: adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. There is good evidence that in early stage (I and II) disease, patients with squamous cell carcinoma have the

best survival after surgical resection but in patients with advanced NSCLC there is no convincing data indicating an association between cell type and response or survival. It is also important to note that intra- and inter-observer (pathologist) reproducibility in classifying the subtypes is relatively poor. However, there is suggestive evidence that NSCLC tumor cells expressing neuroendocrine markers may be more sensitive to chemotherapy than NSCLC tumor cells without such features (Mulshine J et al. Proc ASCO 6:181, 1987).

There are a number of other factors in NSCLC that have prognostic value in this disease. Performance status is extremely important in that response rate is lower and survival shorter in patients with poorer performance status. The presence of extrathoracic metastasis, particularly bone metastasis, is predictive of a lower response rate and shorter survival. Male sex and high LDH values are associated with a poorer overall survival but are not predictive of response rate.

CONCLUSIONS AND RECOMMENDATIONS

Efficacy Endpoints

More recently developed combination chemotherapy regimens have demonstrated a greater degree of activity in the treatment of advanced NSCLC, particularly when compared to that achieved prior to the 1980's. However, response rates, especially in patients with metastatic disease, are still quite low. In addition, an association between response rate and survival has not been convincingly demonstrated. This is probably due to the fact that the proportion of complete responses achieved in NSCLC is still very low. Therefore, **response rate can not be considered a surrogate for survival or quality of life** (which are traditional endpoints used by the FDA for drug approval) in patients with advanced NSCLC. If progress is made to the extent that the response rates (in stage IV disease) are increased to the range of 65-85% and complete response rates are increased to the range of 15-30%, this issue should be re-evaluated.

Response duration and time to tumor progression are currently not acceptable surrogates to survival or quality of life. However, response duration and time to tumor progression may prove to be suitable surrogates if it becomes established that these parameters are associated with reduction in intrathoracic symptoms and/or survival. In regards to end-points, no distinction is made between treatment of primary disease and salvage therapy.

One of the strongest arguments that can be made against focusing solely on surrogates in NSCLC is that they may distract from the goal of developing more effective treatments. Since patients with advanced NSCLC have a relatively short survival, it should not take too long to discover whether a drug is effective based on the evaluation of survival results alone. However, the **other end-points, such as improvement in intrathoracic symptoms and quality of life, may be valuable in determining the overall beneficial impact of a new therapy.** For example, the palliative efficacy of a chemotherapy regimen that causes a slight prolongation in survival may be negated by a significant loss in quality of life. This effect may be related to drug toxicity and should be included in the quality of life assessment. On the other hand, improvement in quality of life may be a sufficient end-point for drug approval under certain circumstances.

The ability of a drug to reduce the incidence of CNS metastasis should also be evaluated. Certainly, a drug with such a property may have a valuable positive impact on survival and quality of life. This issue is an important one since there is evidence to suggest that CNS metastasis will become more common as the survival of patients with NSCLC is extended by otherwise effective treatment.

Relative cost is an important social and medical economic issue that is playing an increasing role in the practice of medicine. However, **the cost of a new treatment is not evaluated**

by the FDA for drug approval. Whether relative cost should be included in the quality of life assessment is controversial.

Controls

The randomized controlled trial is the preferable study design for the approval of drugs in NSCLC. The existence of "standard" effective chemotherapy for advanced NSCLC has not yet been adequately documented. Therefore, it is acceptable to compare a new treatment with an untreated (BSC) control arm. It is understood that participation in such studies in unresectable NSCLC is limited by the reluctance of patients (and their physicians) to participate in trials in which there is a chance of receiving only BSC.

Drugs that have previously been approved by the FDA in the treatment of lung cancer (eg. dactinomycin, doxorubicin, nitrogen mustard) as single agents are unacceptable positive controls for new drug development unless patient benefit has been clearly demonstrated by current standards.

Once an effective drug regimen is established, such a regimen could be used as a positive control for the evaluation of a new drug, in which case the new drug may be approvable if it proves to be equivalent or better than the control regimen.

Blinding studies involving a no treatment or BSC arm could theoretically eliminate problems of surveillance bias. However, it is extremely unlikely that controlled studies in NSCLC can be conducted in a blinded fashion; the reasons for this are obvious and relate mostly to the expected drug-associated side effects as well as other logistics relating to feasibility of adequate blinding and individual IRB policies.

One of the dilemmas in new drug evaluation is to determine the role of the agent when it is used in combination with other treatments. This problem is particularly important in the case of NSCLC where there is a trend to use the most active drugs in combinations. It is preferable that these studies are designed such that the contribution of each of the components in the combination as well as that of the "new" agent can be specifically determined.

Whether neoadjuvant or adjuvant chemotherapy in patients with resectable NSCLC decreases the incidence of local recurrence and distant metastasis and improves overall survival requires further investigation in randomized controlled clinical trials.

Prognostic Factors and Stratification

In the design of clinical trials in NSCLC, there are a number of prognostic factors that should be considered in the randomization, stratification, and post-study analysis scheme. All studies should stratify according performance status and extent of disease (defined by clinical TNM stage) to insure a balance of these two most important prognostic factors. The number of organ systems involved with metastasis, gender,

presence of weight loss, and some assessment of quality of life are other clinical characteristics that should be evaluated.

Since there is no clear association between histological subtype and response or survival in patients with advanced stage NSCLC, a new drug need not be studied separately in each cell type. Currently, demonstration of efficacy in each of the cell types is not necessary for drug approval in NSCLC. However, in early stage (I or II) disease, histologic subtype may be important and, thus, consideration should be given to stratify such patients in adjuvant or neoadjuvant studies according to subtype. However, this approach is not essential. Although observer reproducibility is generally poor, histological subtype, and possibly degree of anaplasia, should be strongly considered in the post-study analysis of all studies. In doing so, more information concerning the significance of these parameters can be obtained. The presence or absence of neuroendocrine markers and oncogene expression should also be considered in the post-study analysis at those institutions where this technology is available.

Whenever possible, pharmacokinetic data should be collected so levels of drug in blood (and possibly, tissue) can be correlated with toxicity and response. The information regarding pharmacokinetic-pharmacodynamic relationships will help to insure that in individual patients a drug will be used in a manner that will yield the maximal therapeutic benefit.

Lastly, FDA recommendations for study design and drug approval in NSCLC are likely to change as our knowledge of this disorder improves. Ongoing basic and clinical research will hopefully lead to a better understanding of the pathophysiology and treatment of this devastating disease.

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