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Current Developments in the Management of Solid Tumor Malignancies

Current Therapies for Glioblastoma

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Has mesothelioma historically been considered as important as it is now?

For many years, mesothelioma was not recognized as an important disease. It is an occupational disease that is related to asbestos exposure, and in the past there was no consistent treatment approach employed throughout the world. There were no data for standard treatment, and no therapy was considered to be especially effective. A few studies achieved prolonged survival through surgery, but the effectiveness was very limited.

Why was mesothelioma not recognized as an important disease?

Mesothelioma is not a very common disease. In addition, in many countries, there were problems related to reimbursement for treatment, because mesothelioma is an occupational disease. In some countries, where the social standards were very high and the disease was recognized as occupational, patients were reimbursed for treatment and, in some cases, their relatives were reimbursed for their living costs after the patients' deaths. In some countries, the industry responsible for the disease had to pay. However, in others countries with lower social standards, this was not the case.

When did attitudes about mesothelioma begin to change?

During the 1960s and 1970s, the widespread understanding that mesothelioma is an important, occupational disease took hold. More recently, people have realized that the destruction of the World Trade Center on September 11, 2001, released a great deal of asbestos into the air, and so mesothelioma could be a significant problem again.

Why have response rates to traditional chemotherapeutic agents typically been lower than 30%?

Thirty percent is very optimistic— typically, it is lower than 10%. There are 2 reasons for this: it is very difficult to document response because of the special growth pattern of this tumor, so evaluation has been a great problem; also, it is a fairly highly differentiated tumor, which makes any kind of tumor-specific therapy difficult. From a biological standpoint, the mesothelioma tumor is related to the soft-tissue sarcomas, which are also not very responsive to chemotherapy.

What are the recent major advances in the treatment of mesothelioma?

For the first time, we now have a standard therapy: cisplatin-pemetrexed (Alimta, Lilly). This combination therapy has recently been approved by the US Food and Drug Administration (FDA); the EMPHASIS study, which provided the basis for this approval, was recently published in the *Journal of Clinical Oncology* by Vogelsang et al. This study was a large, randomized phase III trial that compared single-agent therapy and cisplatin-pemetrexed in combination, and the latter showed significant benefits. This is the only combination therapy for mesothelioma that has been approved, based on phase III data, when before there was no standard chemotherapy. This is an important step forward.

How have recent drugs affected patient quality of life?

All of the new drugs should provide improved quality of life because they may be less toxic, in addition to being effective. The endpoint of improved quality of life is a very important one, but not one that is easy to evaluate. In second-line treatment of non–small-cell lung cancer, pemetrexed was approved partly because it had a favorable toxicity pattern, compared with docetaxel (Taxotere, Aventis).

What other antimetabolites are being evaluated in mesothelioma?

In the past, the antimetabolites were not very popular and in the United States and Western Europe, but in Northern Europe—especially in Sweden, Norway, and Denmark—there has been considerable interest in antimetabolites for some time. For example, methotrexate as a single agent or in combination therapy was considered the standard treatment in Northern Europe before the development of pemetrexed. However, while methotrexate had produced fairly good results, they were not in randomized studies.

Raltitrexed (Tomudex, AstraZeneca) is very closely related to the antimetabolites. It was tested in a phase III trial and produced better results when given in combination with cisplatin, but ultimately the number of patients was too small for the study to be considered conclusive.

There have also been initiatives to investigate gemcitabine (Gemzar, Lilly) in mesothelioma; data on this treatment, including a study presented at the 2004 meeting of the American Society of Clinical Oncology (ASCO), have produced conflicting results. There have been several different phase II studies of gemcitabine in combination and as a single agent, but there has never been a phase III trial.

Edatrexate is another antifolate that may play a role in the treatment of mesothelioma.

Are the antifolates considered targeted agents?

In the sense that there is a treatment target, then yes: pemetrexed targets at least 3 enzyme systems of the folate metabolism. "Targeted therapy" is a very modern term for things we already did 2 decades ago. However, these antifolates are not influencing targets in the way we might use that term today, such as the epidermal growth factor receptor (EGFR), tyrosine kinase inhibitors, monoclonal antibodies, and so on.

Are anti-EGFR targeted agents active in treating mesothelioma?

Gefitinib (Iressa, AstraZeneca) and erlotinib (Tarceva, Genentech) have been investigated in the treatment of mesothelioma, but they were not very successful. This does not mean that anti-EGFR agents will not have a role in treating mesothelioma; we simply do not have enough data yet. Mesothelioma is biologically a very active tumor, and there could be in the future new developments that show targeting agents to be very effective.

What other novel agents are being studied in mesothelioma?

There are ongoing studies of the cyclooxygenase-2 inhibitors in mesothelioma. There also are monoclonal antibodies being investigated in phase I and II studies, but these have not yet reached phase III. There is excitement among investigators to explore new agents in mesothelioma.

Why are there so few agents that have reached phase III trials in mesothelioma, in comparison to other tumor types?

There are practical reasons for this. To obtain approval for a drug, a company has to conduct a large study and determine at the beginning in what disease it is most likely to be successful. Because of the small number of patients with mesothelioma, it is not usually the best place to start this process. Lilly did great work with pemetrexed, and so it was approved for mesothelioma. But as far as small molecules and antibodies are concerned, they have been tested first in other tumors. There is a great need for good treatments in mesothelioma, and it would be certainly wise for drug developers to conduct more studies in this disease.

How have various measures of treatment success changed in recent years?

Because the requirement for getting a drug approved is still to demonstrate that it improves survival compared with the current standard, survival and time to progression are still the most important endpoints of clinical trials for mesothelioma. Survival is still the most valid endpoint, but time to progression may be more important in mesothelioma trials relative to other cancer types, because fewer patients are necessary to obtain valid results, and there are fewer patients with mesothelioma. Response rates also are important as early indicators of a drug's effectiveness before it reaches phase III trials. However, response rates are fairly weak endpoints as far as providing information about a drug's future usefulness.

Now that cisplatin-pemetrexed combination therapy is established as effective first-line therapy, what are next steps that need to be taken in this disease?

Now that there is a standard first-line treatment for this disease, we have to improve inductive treatment for patients with mesothelioma, and we have to develop second-line therapy. At present, there is no standard second-line therapy for mesothelioma, but we know from the EMPHASIS study that there are certain groups of patients who will benefit from second-line therapy. We also have to investigate the indication of chemotherapy in multimodality treatment strategies in this disease, as is already done in other tumors.

We will be looking for predictive and prognostic factors, and we may have new treatment targets, which allows us to develop new drugs. I think traditional chemotherapy will continue to be important in the next years. Improving treatment outcome may not be a matter of chemotherapy alone, but rather may be require a combination of chemotherapy and new biological or molecular therapy. There still are not clear recommendations on how to form these combinations, and so I think chemotherapy has reached a plateau, not only in mesothelioma but also in other tumors.

Since asbestos has been recognized as the cause of mesothelioma for so long, will mesothelioma cease to be a problem?

Despite its relative rarity, mesothelioma needs to stay in the focus of clinical researchers. The production of asbestos ended decades ago, but we will still have an increasing number of patients for approximately 20 years, due to the large gap between exposure to asbestos and disease manifestation. The statistics suggest the peak will be about 2020.

We will also begin to see patients from different occupations. At the beginning, only people in the asbestos industry were affected; now we also realize that other occupations, such as teachers, were also affected, because asbestos was used for insulation in many different types of construction, in houses, schools and others.

Suggested Reading

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003;21:2636-2644.

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