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

ONCOLOGIC DRUGS ADVISORY COMMITTEE DISCUSSION
ON FDA REQUIREMENTS FOR APPROVAL OF NEW DRUGS
FOR TREATMENT OF OVARIAN CANCER

During the meeting of the Oncologic Drugs Advisory Committee on December 8,1987 a discussion of the treatment of ovarian cancer was held in order to explore the known data base regarding the efficacy of current standard therapy. The criteria that should be applied in considering the efficacy of new drugs in this disease was explored. Representatives from the Gynecologic Oncology Group (GOG) were invited to present the data base which has accrued in controlled trials performed by that group in ovarian cancer. Drs. Thigpen and Hosksins represented the GOG. The following is a summary of their presentations and the ensuing discussion by the committee.

The major prognostic variables for prediction of survival are the stage determined at the initial entry into the abdomen and the volume of residual disease after the initial debulking surgery. Staging is performed according to the revised FIGO criteria. Stage 1 and 2 are considered together as limited disease. Low risk patients are those with stage 1A and 1B while those patients in stages 1C and 2 are considered to be at higher risk. Stage 3 and 4 patients are considered together as advanced disease. This group is further divided according to the bulk of disease. Those with stage 3A and 3B (those with tumor nodules less than 2 cm in diameter) are considered to have optimal disease while those with stage 3C and 4 are considered to have suboptimal disease.

The standard surgical approach to patients with ovarian cancer is to perform an exploratory laparotomy through an incision that will allow the inspection of the entire peritoneal cavity. If there is no gross disease multiple biopsies should be taken from various sites within the peritoneal cavity. 24 or more sites are recommended. In this initial surgical approach an attempt to remove as much gross disease as possible (preferably to render the patient free of any tumor nodules >2cm.) is recommended.

Prognosis was shown to be related to the extent of residual disease after surgery in patients who received subsequent single agent melphalan or combination chemotherapy (> or < 2cm) Response rates and survival are both related to the volume of residual disease.

Neither cell type nor histologic grade was documented to be a significant prognostic factor from the GOG data.

Dr. Thigpen summarized the series of investigations performed by the GOG in early ovarian cancer. 79 stage 1A and 1B patients were randomized between post operative melphalan and no further treatment on Study 7601. There were no significant differences in outcome noted between the arms. The projected five year survival in both arms was 96%. For these low risk patients no further treatment is necessary. In study 7602 stage 1C and 2

patients were randomized between postoperative melphalan or ip P32 and no difference was seen in the projected five year survival between the groups, 81%. This 81% five year projected survival was better than that expected from historical controls (50-60%). The gynecologic community has accepted that these patients require post operative therapy and future studies will not employ no treatment control arms. In fact an ongoing study in these patients compares ip P32 with combination chemotherapy consisting of cisplatinum and cyclophosphamide.

He then discussed sequential studies performed by the GOG in patients with stage 3 and 4 disease. Initially the results of therapy in patients treated for bulky disease with single agent melphalan were summarized. The clinical complete response rates in three separate protocols using single agent melphalan were 13, 16, and 17% with an overall median survival of 12 months. Subsequent studies in patients with bulky disease compared melphalan alone to combination chemotherapy.

Study 22 compared melphalan alone to melphalan plus hexamethylmelamine, or to doxorubicin plus cyclophosphamide. Patients had primary stage 3 suboptimal and stage 4 disease. The arm containing doxorubicin and cyclophosphamide had an improved clinical complete response rate but this therapy did not improve overall survival compared with the alternate arms.

Study 47 compared doxorubicin plus cyclophosphamide vs. doxorubicin plus cyclophosphamide plus cisplatinum in patients with stage 3 (residual disease > 3cm) and patients with stage 4 disease. The addition of cisplatinum improved the clinical complete response rate significantly (51 vs. 26%) as well as the median survival (19.7 vs. 15.7 months).

Concurrently studies were being performed in patients with more favorable disease. Study 52 compared cisplatinum and cyclophosphamide vs. these two drugs plus doxorubicin in patients with stage 3 disease with no residual disease > 1 cm. There was no difference in the rate of pathologic complete response (26 vs. 24%; 3 vs. 2 drugs), nor in overall survival. The dose of cyclophosphamide in the double agent arm was twice that given when doxorubicin was added.

Dr. Thigpen then summarized an appropriate approach to the management of patients with ovarian cancer based on these findings and data that appears in the literature. Patients with low risk limited disease should be offered surgery only. High risk limited disease patients should receive post operative adjuvant therapy, preferably intraperitoneal P^{32}. For patients with advanced disease the approach should be a maximal surgical effort to be followed in both optimal and suboptimal patients with cisplatinum based combination chemotherapy. The role of salvage chemotherapy is less clear.

Dr. Hoskins then reviewed this data in an effort to respond to

several questions that were raised by the FDA regarding the whether alternate endpoints can serve as possible surrogates for survival determinations or quality of life assessments. Initially the utility of the complete response rate as a surrogate for overall survival was discussed.

In study 22 patients who had a complete response had an improved median survival. In study 47 the addition of cisplatinum improved both the complete response rate and median survival. In a large study performed in the Netherlands which utilized either CHAP or CP, it was noted that those patients who achieved a pathologic CR and those who had only microscopic disease at second look survived longer than those who achieved a PR, stable disease, or who progressed.

The value of attaining either a clinical or pathologic complete response with different regimens was discussed. Two studies were performed by the GOG in patients with optimal disease. Single agent therapy was investigated in the first and combination therapy was studied in the second. In the first study using single agent melphalan there was a higher percentage of patients progressing during therapy and consequently a lower percentage reached a second look operation. However in those who did not progress on the single agent therapy and went on to second look there was a greater chance of achieving a pathologic CR. On the combination therapy arms (CP or CAP) there were more patients achieving a clinical CR but less of these were confirmed at the second look. This suggested that the finding of a clinical CR may have different impacts upon overall outcome using different regimens.

A literature review was conducted by Dr. Hoskins that examined the outcome of over than 1000 patients with ovarian cancer who underwent second look surgery. The chance of achieving a negative second look was related to stage, grade, and residual disease after surgery. The overall recurrence rate of those who achieved a pathologic CR was 19%. The recurrence rate in stage 3 and 4 was 26%. The rate in a subgroup consisting of those with stage 3, grade 3 and 4 was as high as 50%. This general pattern of the risk of recurrence after a negative second look was confirmed by data collected at Memorial Sloan Kettering Institute. At Memorial when patients with negative second look operations were compared based on whether they received platinum containing chemotherapy additional findings were seen. Firstly, the duration of treatment prior to the second look differed according to whether the patients received platinum containing regimens or not (10 vs. 20 months). Secondly, there was a significantly longer relapse free period after negative second look in those treated with non platinum containing regimens. This may reflect the fact the the clinical CR rate is higher for the platinum regimens and the fact that the second look surgery was performed earlier in these patients. The patients who were destined to fail on non platinum regimens may have already failed prior to having reached the time when second look surgery was to

be performed. A significant proportion of the patients who achieve a negative second look operation on platinum containing regimens ultimately failed. These failures were noted to occur relatively early. 80% of the failures occured in 2 years and 90% in 3 years. In these patients a negative look operation that persisted for 2-3 years correlated with survival.

These data were further discussed by members of the committee and several questions were raised. Among these were the following. The value of combination chemotherapy vs. single agent therapy in patients with bulky disease was questioned. Conflicting studies are difficult to compare because of differences in dose intensity of the regimens that have been studied. The uniformity of pathologic restaging across various centers has not been demonstrated and so interstudy differences are difficult to interpret. The correlation between complete clinical response and overall survival is less clear than the correlation of pathologic complete response and overall survival.

A primary question considered by the committee was whether the demonstration of similar rates of clincial complete response or histologically negative second look exams can lead to the conclusion that overall survival will be similar when two drugs or two regimens are compared. Dr. Temple summarized the sense of the discussion. A marked improvement compared to a controlled therapy in either complete clinical response or pathological response could serve as a basis for approval. Data would then be collected on disease free interval and survival for subsequent confirmation of treatment benefit. The demonstration of the equivalence of complete clinical response or pathologic response would require that additional data regarding the duration of response (or survival) up to a point(2 to 5 years) would be required prior to approval. If this type of data was available in one adequate and well controlled study and it is confirmed that equivalent response rates correlate in that study with equivalent overall survival rates, the second study needed for approval could rely upon a demonstration of equivalent response rates when the test regimen is compared with a known effective regimen.

The committee stressed that the application of these principles regarding the use of response rate data as surrogates for survival can not to be generalized to additional tumor types. Each tumor must be individually considered.

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