HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM-CELL SUPPORT FOR TREATMENT OF MULTIPLE MYELOMA IN OLDER PATIENTS

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OBJECTIVE

Conventional chemotherapy for multiple myeloma will induce responses in most newly diagnosed and many relapsed patients. Nonetheless, repeated recurrences and the development of resistance ultimately result in the death of more than 95% of myeloma patients within 10 years of diagnosis. Evidence reviewed in a previous Technology Evaluation Center (TEC) Assessment (vol. 11, no. 14, 1996) showed that high-dose chemotherapy (with or without radiation) followed by autologous stem cell support (HDC/AuSCS) using cells from either bone marrow or peripheral blood improves health outcomes (event-free and overall survival) for patients with multiple myeloma that is not refractory to conventional-dose treatment. This includes both newly diagnosed patients and those who have relapsed some time after responding to induction therapy. However, nearly all studies on HDC/AuSCS reviewed for the previous technology assessment excluded patients older than 65 years. Few patients older than 60 years were enrolled in these trials, with median ages in most series ranging from 48 to 57 years.

More than 50% of patients with multiple myeloma are older than 65 years at diagnosis. There are concerns that older patients (i.e., mid-sixties and above) may be less able than younger patients (i.e., mid-fifties) to withstand or recover from the toxicities of myeloablative treatment regimens. Another concern is that blood or marrow stem cells from older patients may be less able than stem cells from younger patients to restore normal hematopoiesis rapidly and completely after HDC/AuSCS.

This technology assessment examines the available evidence on the health outcomes of HDC/AuSCS for the treatment of multiple myeloma in older patients. Comparisons will be made to available evidence on health outcomes of conventional-dose management of myeloma in similar patients, and to health outcomes of HDC/AuSCS in younger patients. To update the previous assessment, new evidence from comparative trials on younger patients also will be summarized. In addition, the Background section will review information on myeloma in older patients.

BACKGROUND

Epidemiology

Multiple myeloma is a systemic malignancy of relatively well-differentiated plasma cells (B-lymphocytes) that accounts for approximately 10% of hematologic cancers and for approximately 10,000 deaths annually in the United States (Alexanian and Dimopoulos 1994, 1995; Choy et al. 1995; Foerster and Paraskevas 1999; San Miguel et al. 1999; Desikan et al. 1999). The incidence of myeloma is between 1 and 2 cases per 100,000 in the Caucasian population, and approximately twice that among African-Americans. Approximately 60% of patients are male. The incidence increases with age: mean age at diagnosis was reported to be 62 years, median age at diagnosis was reported to be 69 years, and fewer than 2% of patients are

less than 40 years old (Foerster and Paraskevas 1999; Pileri et al. 1993; Gautier and Cohen 1994).

Diagnosis

Multiple myeloma usually is characterized by the presence of an intact or fragmented monoclonal immunoglobulin in the serum or urine, attributable to the B cell-derived tumor population. Presenting signs and symptoms include bone pain, weakness, anemia, and infection (Salmon and Cassady 1997; Foerster and Paraskevas 1999). Major criteria to establish the diagnosis of multiple myeloma are plasmacytomas on tissue biopsy, bone marrow plasmacytosis (>30%), and electrophoretic detection of the monoclonal immunoglobulin protein. Additional criteria also may contribute to establishing the diagnosis (for review, see Anderson 1993; Salmon and Cassady 1997; Foerster and Paraskevas 1999). Monoclonal gammopathy of unknown significance (MGUS), smoldering myeloma, and indolent myeloma are among the other conditions associated with the presence of a monoclonal protein in the serum that must be distinguished from multiple myeloma (for review, see Cohen 1985; Kyle 1987; Gautier and Cohen 1994).

Staging and Prognostic Factors

Various systems have been proposed for staging multiple myeloma. The Durie/Salmon system, which relies primarily on inferred tumor cell mass (body burden), is most commonly used. Three stages (I, II, III) are defined in this system, which correspond to low, intermediate, and high tumor mass as measured by changes in hemoglobin, serum calcium, M-component production (IgG, IgA, κ- or λ-urine light chain), and the presence of advanced lytic bone lesions. Survival duration is correlated with Durie/Salmon stage at diagnosis. Within stages, patients are frequently subclassified 'A' or 'B' based on normal or abnormal renal function, respectively. Historically, patients in stage IA have median survival of 5 years; those in stage IIIB (the most advanced stage) have median survival of only 15 months (Kyle 1994).

Other factors have independent prognostic value for the duration of survival after diagnosis of multiple myeloma. The myeloma cell proliferative rate, most often measured by labeling index is among the most useful prognostic factors. Serum concentration of β_2-microglobulin (β_2-M), which also is valuable, appears to be a proxy variable for tumor mass (Kyle 1994; Seiden and Anderson 1994). Survival curves were divided more effectively into groups with a good or a poor prognosis by the combination of these two variables than by any other combination of prognostic factors (Greipp et al. 1993).

Genetic analysis has not demonstrated a consistent chromosomal abnormality or any alteration in the coding sequence or expression of an oncogene or tumor suppressor gene in association with multiple myeloma (Seiden and Anderson 1994). However, certain candidate chromosomal abnormalities appear to provide useful prognostic information (Tricot et al. 1995; Tricot et al. 1997). These include translocations or deletions on chromosomes 11 or 13.

Multivariate analysis also has identified prognostic variables that independently predict the duration of survival after HDC/AuSCS. Generally, these are the same as those found to be

statistically significant predictors after conventional-dose therapy (San Miguel et al. 1999). Favorable characteristics include low β_2-M (≤2.5 mg/L) and either less prior therapy, fewer previous regimens, or a shorter time from diagnosis to transplant. Additional factors have been shown to be independently favorable in some but not all studies. These include low serum concentrations of C-reactive protein (≤4.0 mg/L), a monoclonal immunoglobulin isotype other than IgA, the absence of an unfavorable karyotype by cytogenetic analysis (Jagannath et al. 1997; Tricot et al. 1997), and a complete remission prior to transplant (Bjorkstrand et al. 1994; Alegre et al. 1998). Age (younger than 50 years), performance status (ECOG less than 2), and Durie-Salmon stage (less than III) were significant positive predictors in univariate analyses, but not in multivariate analysis. Studies disagree on the significance of the myeloma cell labeling index, which is a significant prognostic factor for survival after conventional-dose therapy. One study reported that a high labeling index did not predict for shortened survival after HDC/AuSCS (Boccadoro et al. 1997), while another study found it did (Gertz et al. 1997).

Treatment

Standard management of myeloma is related to stage at diagnosis (Samson 1994; Alexanian and Dimopoulos 1995; Choy et al. 1995; Foerster and Paraskevas 1999; San Miguel et al. 1999; Desikan et al. 1999). Patients with MGUS or smoldering myeloma are asymptomatic, may not progress, and do not have survival increased by early treatment (Kyle and Greipp, 1980; Cohen 1985; Kyle 1987; Gautier and Cohen, 1994). Those with indolent myeloma may have up to three bone lesions but no fractures or other associated features or symptoms, and also should not be treated until symptoms develop or the disease progresses. Initial management of low-tumor mass (Stage I) disease also may be limited to observation and treatment of symptoms.

Patients diagnosed with more advanced disease (Stage II or III) undergo systemic cytotoxic therapy, typically intermittent melphalan/ prednisone (MP) (Gregory et al. 1992; Foerster and Paraskevas 1999; San Miguel et al. 1999; Desikan et al. 1999). Patients with progressive disease or resistance to MP may be treated with high-dose dexamethasone as a single agent, but usually undergo chemotherapy with combinations of agents, such as vincristine, doxorubicin and dexamethasone without (VAD) or with carmustine (VBAD), vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) or variants of these combinations. In recent years, these more aggressive regimens also are being used with increasing frequency as first-line induction therapy and as initial treatment for myeloma that has relapsed after a long remission. Available review articles estimate that with conventional-dose chemotherapy, median survival by stage at diagnosis is greater than 60 months for those with stage I, approximately 41 months for those with stage II, and approximately 23 months for those with stage III (Salmon and Cassady 1997; Foerster and Paraskevas 1999; San Miguel et al. 1999; Desikan et al. 1999).

Evidence reviewed in a previous TEC Assessment (BCBSA 1995) supported the conclusion that alpha-interferon (IFNα) increases the duration of survival for patients with myeloma when administered as a component of first-line therapy for either induction or maintenance of remission. Some patient subsets (e.g., those with IgA or Bence-Jones myeloma) appear to be more likely than the general population of myeloma patients to have the duration of survival or disease-free survival increased by IFNα treatment.

Single High-Dose Chemoradiotherapy with Autologous Stem-Cell Support (HDC/AuSCS)

The following considerations provided a rationale for the hypothesis that HDC/AuSCS might improve outcomes for patients with multiple myeloma when compared with the outcomes of conventional-dose therapy. Despite extensive research, even the most aggressive current regimens of conventional-dose chemotherapy do not cure substantial numbers of patients. Many malignancies, including multiple myeloma, display a steep chemotherapy dose-response curve. Escalating the dose beyond hematologic tolerance thus increases tumor cell kill. Based on this rationale, clinical studies of HDC with stem-cell support were undertaken in multiple myeloma patients (Barlogie 1991; Barlogie and Gahrton 1991; Jagannath et al. 1994; Barlogie et al. 1995; Mohrbacher and Anderson 1995). Various regimens have been used in these studies, generally including one or more alkylating agents, alone or with total body irradiation.

The earliest studies of stem-cell transplantation in myeloma patients used allogeneic bone marrow cells to restore hematopoiesis after HDC. However, the relatively advanced age of most myeloma patients increased their susceptibility to graft-versus-host disease and treatment-related mortality and morbidity. Evidence reviewed in a previous TEC Assessment (BCBSA 1997) was judged insufficient to establish that allogeneic transplantation improves health outcomes for patients with either newly diagnosed, responsive, or refractory myeloma. Additionally, in a high priority trial sponsored by the U.S. National Cancer Institute (SWOG-9321/INT-0141) to compare conventional-dose therapy with HDC/AuSCS and with allogeneic transplantation for patients with multiple myeloma, the allogeneic transplant arm was permanently closed in August, 1997 due to excessive treatment-related morbidity and early mortality.

Initially, some clinicians hesitated to investigate autologous bone marrow transplantation, as marrow from myeloma patients prior to transplant presumably contains malignant plasma cells. Despite the hypothesis that reinfused myeloma cells may contribute to relapse, residual malignant cells in the patient probably cause relapse more frequently. Nevertheless, chemical purging of autologous marrow was studied in an effort to reduce the tumor cell population in the product infused (Anderson et al. 1991; Anderson et al. 1993; Rhodes et al. 1992; Reece et al. 1993; Dimopoulos et al. 1993; Seiden et al. 1995). Due to injury of the stem cell population, however, chemically purged bone marrow cells usually take longer to restore blood cell counts and are associated with a higher rate of death from infection, and even of graft failure, than unpurged bone marrow cells.

An alternative approach is the use of autologous peripheral blood stem cells. It appears that these cells are less likely than marrow to be contaminated with malignant plasma cells (Fermand et al. 1992, 1995a, 1995b; Reiffers et al. 1992; Dimopoulos et al. 1994; Gianni et al. 1994; Alegre et al. 1995; Tricot et al. 1995). Stem cells were mobilized into the circulation in the recovery phase after chemotherapy, and were harvested by cytapheresis. Peripheral blood stem cells also appear to produce more rapid engraftment, shortening the duration of aplasia. Recently, this approach has been extensively investigated (e.g., Demirer et al. 1996, Millar et al. 1996, Raje et al. 1997). Peripheral blood, with mobilization using chemotherapy followed by myeloid growth factors, has largely replaced marrow as the source of stem cells to transplant into myeloma patients (Kyle 1999). Selecting circulating hematopoietic stem cells for reinfusion by cell surface antigen phenotype, presumably further reducing myeloma cell contamination of the

graft, is a newer technology under investigation (Strauss et al. 1991; Schiller et al. 1995; Johnson et al. 1996; Harousseau 1999a). Differential mobilization into peripheral blood of normal versus malignant marrow cells is an intriguing observation that requires extension and confirmation (Gazitt et al. 1996). However, it remains to be determined if chemical purging or positive stem cell selection either increases survival or reduces relapses after HDC/AuSCS for multiple myeloma.

In 1996, a TEC Assessment concluded that evidence was sufficient to support the conclusion that HDC/AuSCS improves outcomes, including the duration of survival and disease-free survival, for patients with newly diagnosed or responsive myeloma, when compared with conventional-dose therapy (BCBSA 1996). One objective of this Special Report is to update the earlier evaluation of HDC/AuSCS as therapy for myeloma with any new evidence from controlled studies. Note that both the original Assessment (BCBSA 1996) and a subsequent re-evaluation (BCBSA 1998a) found the available evidence insufficient to support conclusions regarding the outcomes of HDC/AuSCS for patients with resistant or refractory myeloma.

Tandem High-Dose Chemoradiotherapy with Autologous Stem-Cell Support (TanHDC/AuSCS)

Despite the increased duration of remission and survival after HDC/AuSCS when compared with conventional-dose management, the majority (≥75%) of patients with advanced myeloma eventually relapse (Harousseau and Attal 1997; Kovacsovics and Delaly 1997; Schlossman and Anderson, 1997; Kyle 1999; Harousseau 1999b). This has been cited as evidence of residual malignant plasma cells in the patients. Eradicating residual tumor cells before relapse is detected using multiple rounds of intensive chemotherapy with intensive supportive care, often referred to as tandem transplants (TanHDC/AuSCS), has been proposed as a potentially curative approach (Desikan et al. 1999; Barlogie et al. 1997, 1999).

TanHDC/AuSCS is the planned administration of two or more cycles of intensive chemotherapy, alone or with total body irradiation, each of which is followed by reinfusion of autologous hematopoietic stem cells. The second (or subsequent) cycle(s) is given with the intent of further cytoreduction and in the absence of any evidence of tumor progression or relapse. Cycles of TanHDC/AuSCS are generally administered at intervals of 2–6 months, contingent on recovery from prior toxicity.

TanHDC/AuSCS has been investigated in patients with myeloma (Desikan et al. 1999; Barlogie et al. 1997, 1999), as well as in those with other cancers (Patrone et al. 1995; Bitran et al. 1996; Lotz et al. 1996; Ayash et al. 1996; Shapiro et al. 1997). In the earliest study on myeloma, only the second of two intensive treatments was followed by stem-cell reinfusion (Harousseau et al. 1992). Toxicity was excessive with this approach, due to inadequate hematologic recovery after the first course. More recent studies in which multiple intensive treatments were each followed by stem-cell reinfusion were reviewed separately in two recent TEC Assessments for patients with newly diagnosed or responsive myeloma (BCBSA 1998b) and for patients with resistant myeloma (BCBSA 1998a). An interim analysis on half the patients enrolled is the only report thus far from the one randomized trial that compares outcomes of tandem transplants with outcomes of single transplants (Attal et al. 1997b). Thus, both TEC Assessments concluded that

evidence was insufficient to determine if TanHDC/AuSCS improved outcomes compared with those of single HDC/AuSCS.

This technology assessment compares outcomes of HDC/AuSCS with those of conventional-dose chemotherapy in older patients. Because the data on HDC in older patients is limited, this assessment also includes outcomes of TanHDC/AuSCS. The comparison of TanHDC/AuSCS to single HDC/AuSCS is outside the scope of this assessment.

Treatment of Malignancy in Older versus Younger Patients

Aging is accompanied by progressive changes in organ and cellular function that can affect many aspects of cancer treatment and prognosis (see Balducci, Lyman and Ershler 1998; Balducci and Extermann 2000 for reviews). However, individuals vary considerably with respect to the rate at which these changes occur (Duthie 1998; Balducci and Extermann 2000). This has lead to the concept of physiological age, in contrast to chronological age. Additionally, because the changes that accompany aging are progressive, it is often useful to subdivide "older" patients with cancer into groups that are more homogeneous. An approach used frequently refers to the young-old (mid-sixties to mid-seventies), the old-old (mid-seventies to mid-eighties), and oldest old (late eighties and above).

Multiple factors may mediate the effects of aging on prognosis and response to treatment for patients with a malignancy. Cells from tumors that occur in older and younger patients may differ in their intrinsic biologic behavior (see Duthie 1998; Holmes, 1998; and Balducci and Extermann 2000 for reviews). These differences may be in opposite directions for different malignancies. For example, breast cancer that occurs in older women is generally more indolent, more frequently well-differentiated and positive for estrogen and/or progesterone receptor, and usually has a more favorable prognosis than breast cancer in young women. The opposite is true for acute myelogenous leukemia, for which older patients have a less favorable prognosis than younger patients. This may partly result from more frequent over-expression of the multi-drug resistance gene and a higher prevalence of unfavorable cytogenetic changes in the older patients.

Older and younger patients also may differ in their responses to treatment with chemotherapy, radiation or both (see Kimmick et al. 1997 Cova et al. 1998; Scalliet and Pignon 1998; Balducci and Corcoran, 2000; and Zachariah and Balducci, 2000 for reviews). Some of these differences may be due to intrinsic differences in gene expression (e.g., the multi-drug resistance gene mentioned above) or other factors that alter responses at the cellular level. Changes in organ function may alter the absorption, distribution, metabolism or excretion of drugs. Depending on the specific drug and the specific physiological change, aging may either increase or decrease tumor or normal cell exposure to the drug or its biologically active metabolites.

For example, slower hepatic metabolism may reduce the efficacy of drugs that require metabolic activation, but may increase biological half-life for drugs that are metabolized and inactivated before they are cleared by the kidney. The effectiveness and/or toxicity of radiation therapy may be altered because blood circulation and tissue oxygenation may be decreased in older patients. Circulatory changes in older patients that affect tissue perfusion also may affect drug exposure for tumors of solid tissues or organs. Factors such as renal function and the relative volumes of

body water and fat in which drugs are distributed are known to change with aging and can alter the clearance and concentrations *in vivo* of chemotherapy drugs. Thus, older and younger patients may differ with respect to drug efficacy as well as drug toxicity. In general, the window between therapeutically effective and excessively toxic concentrations of chemotherapy drugs is probably more narrow in older patients and in those with impaired renal function. Nevertheless, dose adjustments based on factors such as clearance rates can be used to administer safe and effective chemotherapy in older patients (Gelman and Taylor 1984; Kimmick et al. 1997; Zagonel et al. 1998).

Older patients also may be less able to tolerate the side effects of drugs or radiation even when these do not occur with an increased frequency or severity (see Kimmick et al. 1997; Duthie, 1998; Zagonel et al. 1998; Exterman and Balducci 1998; and Balducci and Corcoran, 2000 for reviews). For example, recovery from damage to the gastrointestinal tract may be delayed in older patients, resulting in increased susceptibility to mucositis. Bone marrow toxicity is dose limiting for many chemotherapy drugs. Bone marrow stem cell reserve capacity, which can affect the rate of recovery from marrow toxicity, may decline with aging (Moscinski 1998a, 1998b).

Bone marrow stem cell reserve capacity is particularly relevant to use of HDC/AuSCS in older patients. Conversion of cellular "red marrow" to fatty "yellow marrow" progresses with aging at a rate approximating 1% per year up to age 80 (Moscinski 1998a). With time, marrow cellularity is limited to portions of the vertebral column and sternum, ribs, pelvis, and parts of the humerus and femur. This may affect the success of bone marrow stem cell harvests from older patients. The capacity of hematopoietic stem cells for self-renewal and/or proliferation may decline with age (Moscinski 1998b; Fields et al. 1998). Additionally, mobilizing stem cells from the bone marrow into the peripheral circulation for harvest by leukapheresis may be more difficult in older patients. Although it is not a concern for autologous transplantation, the increasing incidence and severity of graft-versus-host disease with the recipients' age severely limits the use of allogeneic transplantation in older patients (Fields et al. 1998).

Patients in the Medicare population are heterogeneous with respect to all of the factors discussed in this section. It is unlikely that the risks of either conventional-dose therapy or HDC/AuSCS are the same for the "young-old" as for the "oldest old." Thus, the concept of physiological age must be stressed as an important element in selecting candidates for either treatment alternative.

Myeloma in Older Patients

Studies disagree on whether age is an independently significant prognostic factor for patients with multiple myeloma (see Gautier and Cohen 1994; Ballester et al. 1998 for reviews). Some studies report a worse prognosis for older patients, while others find no difference in prognosis for older and younger patient groups. Patient selection may explain the disagreement among studies. Gautier and Cohen (1994) suggest that community-based studies, which usually collect data on all patients with the disease in a given geographical area, tend to include sicker patients with a greater incidence of comorbid diseases. These studies generally report a significantly poorer prognosis for older patients, who also tend to have a greater incidence of comorbid diseases. Studies that analyze data only from tertiary referral centers or prospective clinical trials

tend to include patients with better performance status and fewer comorbid conditions. These studies generally report no significant effect of age on prognosis.

The incidence and severity of complications from multiple myeloma tend to be greater in older than in younger patients (Cohen 1985; Kyle 1987; Pileri et al. 1993; Gautier and Cohen 1994). These include hypercalcemia and lytic bone lesions, infections, renal failure, hyperviscosity, anemia, and spinal cord compression resulting in neurologic complications. Initial diagnosis of myeloma in older patients also may be more difficult since some presenting findings, such as pain from bone lesions or hypercalcemia, frequently occur in the elderly from other etiologies. Managing the complications from multiple myeloma also may be more difficult in older patients. For example, older patients may be more susceptible to infections, possibly due to a weakened immune system. Nevertheless, these difficulties are less likely a direct result of chronological age than of physiological age. It has not been shown that older patients with myeloma, who are otherwise in good physical condition and general health, are more likely to suffer from these complications of the disease than younger patients in comparable physical condition.

Many patients are in their sixties or seventies, and some are in their eighties, when initially diagnosed with multiple myeloma. Thus older patients with myeloma frequently are in either the "young-old" or "old-old" subgroups. Rarely, patients in the "oldest old" subgroup may be diagnosed with myeloma. As will be shown in the Review of Evidence below, virtually all older myeloma patients treated with HDC/AuSCS in the studies identified for the technology assessment were in the "young-old" subgroup at the time of transplant.

FDA Status

Because high-dose chemotherapy with autologous stem-cell support is a procedure, it is not subject to U.S. Food and Drug Administration (FDA) regulation. The cytotoxic drugs used in high-dose chemotherapy do require and have received FDA approval. As administered in high-dose chemotherapy, these drugs may be applied outside of the FDA-approved labeled doses and indications(s).

The FDA considers devices and chemical agents used for in vitro purging of stem cells from bone marrow or peripheral blood, or for positive selection of stem cells from bone marrow or peripheral blood, to be subject to regulatory approval (*Federal Register,* 1993; 58(197):53248-51). The only device cleared for marketing in the U.S. for use in stem-cell separation is the Isolex® 300 and Isolex® 300i magnetic cell selection system (Nexell Therapeutics, Inc., Irvine, CA) for "processing autologous peripheral blood progenitor cell (PBPC) products to obtain a CD 34+ cell enriched population intended for hematopoietic reconstitution after myeloablative therapy in patients with CD 34-negative tumors." This system received clearance to market via premarket application (PMA) approval on July 2, 1999.

METHODS

Search Methods

Studies of treatment for multiple myeloma were identified primarily through a computerized search of the MEDLINE database from 1995 through February 2000. The search utilized the Medical Subject Headings (MeSH terms) "multiple myeloma" linked with "hematopoietic stem cell transplantation" or "bone marrow transplantation." Results of the search were limited to papers published in English that described clinical studies on human patients. Searches of *Current Contents* and examination of reference lists from key papers complemented the MEDLINE literature searches. Abstracts of the American Society of Hematology meeting were reviewed, and syllabus material from the VI International Workshop on Multiple Myeloma (June 1997) was obtained. Attendance at scientific meetings, and discussions with leading investigators in the field served to identify recent and ongoing trials.

Study Selection

The literature search identified approximately 240 papers in English language indexed to multiple myeloma and HDC/AuSCS. Studies that included a control group managed with conventional-dose therapy and reported on ≥10 patients in each arm were selected for this assessment to update the earlier TEC Assessment on HDC/AuSCS for myeloma (BCBSA 1996). Studies with or without control groups were selected to compare outcomes of HDC/AuSCS with outcomes of standard-dose regimens for older patient with myeloma and to compare outcomes in older and younger patients with myeloma if they:

- reported outcomes for homogeneous patient groups with respect to age (either less than 60 years versus ≥60 years or less than 65 years versus ≥65 years); and
- reported on ≥10 patients per group.

The following types of studies were excluded from analysis in this Assessment:

- studies that did not provide outcome data on at least 10 patients;
- studies that enrolled patients with resistant or refractory myeloma;
- studies that aggregated results for patients transplanted as part of first-line therapy for myeloma with results for those transplanted as salvage therapy for resistant disease;
- studies that aggregated results of resistant patients with those of chemosensitive patients or previously untreated patients;
- except to compare outcomes in older and younger patients with myeloma, studies in which the preparation and engraftment of the stem-cell population was the focus of the paper and in which no survival data were reported;
- studies of chemotherapy re-induction in which only a minority of patients actually went on to intended HDC/AuSCS;
- multiple reports on the same patients (in such cases, the publication containing the most clearly presented data, not necessarily the latest date, was selected).

Additional Sources of Data

The published evidence was supplemented with unpublished data from the following sources. Dr. M. Attal (Hôpital Purpan, Toulouse, France) provided an update of results from a published French multicenter randomized trial comparing HDC/AuSCS with conventional-dose therapy. Dr. M. Boccadoro (Ospedale Molinette and Università di Torino, Torino, Italy) provided a

subgroup analysis of patients ≥65 years old from a published study that compared the outcomes of up to three cycles of HDC/AuSCS with those of conventional therapy in matched controls. Drs. B. Barlogie, G. Tricot and colleagues (Arkansas Cancer Research Center and University of Arkansas for Medical Sciences, Little Rock, AR) provided an analysis of all patients with less than 8 months of prior therapy treated at their center. This analysis compared outcomes of TanHDC/ AuSCS for patients aged ≥65 years to outcomes for those aged less than 65 years. The Statistical Center of the Autologous Blood and Marrow Transplant Registry (ABMTR; Milwaukee, WI) provided an analysis of all patients reported to the registry with myeloma that was not progressing at transplant. This analysis, which has not been reviewed or approved by the Advisory Committee of the ABMTR, compared outcomes of HDC/AuSCS for patients older than 60 years with outcomes for patients aged 50–60 years. Dr. J. Crowley and colleagues of the Southwest Oncology Group (SWOG) Statistical Office (Seattle, WA) provided an analysis of data pooled from three published SWOG randomized trials of conventional-dose therapies. This analysis compared outcomes for patients aged 65-74 years with those for patients aged less than 65 years.

FORMULATION OF THE ASSESSMENT

Patient Indications

Disease. Patients with newly diagnosed or responsive multiple myeloma. This includes those with previously untreated disease, those in a complete or partial remission, and those in a responsive relapse.

Age. In this assessment, the term "older patients" refers to those whose age ranges from the mid-sixties to the mid-seventies. The oldest patient treated with HDC/AuSCS for myeloma included in the evidence found for this assessment was 77 years old. In contrast, most study populations in trials of HDC/AuSCS have been in their mid- to late fifties or younger.

Technologies to be Compared

High-Dose Chemotherapy with Autologous Stem-cell Support (HDC/AuSCS). HDC/AuSCS is one or more cycles of systemic chemotherapy at myeloablative doses using one of various regimens with or without total body irradiation. Each cycle is followed by autologous stem-cell support to restore hematopoietic function, using cells harvested before the first cycle from either bone marrow or peripheral blood. This assessment does not distinguish data on the outcomes of single HDC/AuSCS from data on TanHDC/AuSCS; with each, patients are treated at least once with myeloablative doses and must be rescued with hematopoietic stem cells.

Alternative Treatments. The most widely used conventional options for therapy of multiple myeloma for patients with newly diagnosed multiple myeloma is induction chemotherapy with an alkylator (usually melphalan) plus a glucocorticoid (usually prednisone, "MP" therapy) or with a multi-drug regimen. Evidence reviewed in a previous TEC Assessment (vol. 10, no. 16) supported the conclusion that IFNα increases the duration of survival for patients with myeloma when administered as a component of first-line therapy for either induction or maintenance of remission. Other alternatives for post-induction management include maintenance chemotherapy

(with MP or carmustine plus prednisone) or observation until relapse occurs. There are two conventional treatment options for patients who relapse after a lengthy remission. These are induction with the same or a more aggressive regimen as that used for primary therapy, and observation or maintenance with IFNα or chemotherapy after induction for those who respond.

Health Outcomes

The main health outcome HDC/AuSCS is intended to improve is duration of survival by directly altering the course of myeloma or by increasing the time to relapse or progression thereby forestalling the natural progression. However, death from unrelated causes is more frequent among patients with mean age 10-15 years older. Therefore, disease-free or progression-free survival may be more useful than overall survival to compare outcomes of HDC/ AuSCS for older and younger patients. These also may be more useful than overall survival for comparing outcomes of HDC/AuSCS with those of conventional treatment in the older patients.

HDC/AuSCS also might improve quality of life if it increases the duration of time without symptoms or decreases the need for additional treatment. One quantitative approach that has been used to address this is to compare patients groups treated with each alternative with respect to the average time without symptoms, treatment, or treatment-related toxicity (TWiSTT) (Cole et al. 1994). Adverse health outcomes of HDC/AuSCS are treatment-related morbidity and mortality.

Specific Assessment Questions

A. Does recent evidence from comparative studies confirm the earlier conclusion that HDC/AuSCS improves health outcomes in younger patients with multiple myeloma?

B. In older patients with myeloma, does HDC/AuSCS improve health outcomes compared to conventional-dose treatment?

C. Do older patients with myeloma obtain a benefit from HDC/AuSCS that is similar to that obtained by younger patients?

REVIEW OF EVIDENCE

A. Does recent evidence from comparative studies confirm the earlier conclusion that HDC/AuSCS improves health outcomes in younger patients with multiple myeloma?

The literature search found no new randomized trials comparing HDC/AuSCS to conventional-dose therapy, and the Intergoupe Française du Myélome trial (IFM-90) remains the only randomized study available (Attal et al. 1996). In this study, mean age was 57.4±6 years for all patients enrolled, and was 58±5 and 57±6 years in the control and HDC/AuSCS arms, respectively. Data at 40 months median follow-up were reviewed in a previous TEC Assessment (BCBSA 1996). Kaplan-Meier analysis showed that median event-free survival (EFS, 27 versus 18 months), median overall survival (>40 versus 37 months) and overall survival at 5 years after diagnosis (52% versus 12%) were greater in the HDC/AuSCS arm than in the control arm.

Published updates at 60 months median follow-up report that projected EFS at six year (24% versus 15%; p=0.01; median, 28 versus 18 months) and projected overall survival at 6 years (43% versus 21%; p=0.03; median, 57 months versus 42 months) remain significantly better in the arm given HDC/AuSCS (Attal et al. 1997a, 1998). An unpublished update with 70 months median follow-up for patients still alive projects overall survival at seven years to be 40% in the arm given HDC/AuSCS and 15% in the control arm ($p<0.05$; Attal 1999, unpublished data). In addition, the estimates of median survival remain 57 and 42 months with an additional year of follow-up. Although slightly smaller than in the original report, the differences in outcome between the HDC/AuSCS and control arms remain statistically and clinically significant and favor the HDC/AuSCS arm.

Table 1 summarizes data from three comparative trials published since the 1996 TEC Assessment. One of these is a non-randomized population-based study conducted by the Nordic Myeloma Study Group (Lenhoff et al. 2000). This study prospectively registered 348 patients with myeloma, which represents 77% of the total expected in the population served by the participating centers based on previous incidence studies, of whom 274 (61%) received HDC/AuSCS. The median age for this group was 51 years, and all patients were less than 60 years old. Outcomes for these patients were compared with those for 313 historical controls managed with conventional-dose therapy, or 76% of the total expected for the population, of whom 274 were matched for eligibility criteria specified in the HDC/AuSCS protocol. Note that outcomes were reported for both the complete registered populations and for the matched groups who received or were eligible for transplant; Table 1 summarizes results for each pair of patient groups. Data from this study demonstrated longer survival for the prospectively registered transplant population compared with the historical population (risk ratio for the historical population, 1.46; 95% CI, 1.14 to 1.86). The duration of survival also was longer for the group given HDC/AuSCS than for the control group eligible for transplant (risk ratio for the control group, 1.62; 95% CI, 1.22 to 2.15).

A trial conducted by the Myélome Autogreffe group randomized newly diagnosed patients with myeloma to treatment with HDC/AuSCS immediately after three or four courses of conventional-dose induction therapy (early HDC/AuSCS arm), or to a total of six courses of conventional-dose induction followed by HDC/AuSCS only if the disease relapsed or failed to respond (late HDC/AuSCS arm) (Fermand et al. 1995a, 1995b, 1998). All patients were less than 56 years of age.

Median event-free survival for patients in the early HDC/AuSCS arm was 39 months while the median interval to failure of induction or death in the late HDC/AuSCS arm was 13 months. The investigators also analyzed the average time without symptoms, treatment or treatment-related toxicity (TWiSTT) in each arm over a median follow-up duration of 58 months. The average TWiSTT was reported to be 27.8 months (95% CI, 23.8 to 31.8) for the early HDC/ AuSCS arm and 22.3 months (95% CI, 16.0 to 28.6) in the late HDC/AuSCS arm. There was no difference in overall survival between the two arms.

Table 1. Recent Studies that Compare Outcomes of HDC/AuSCS to Outcomes of Conventional-Dose Therapy for Newly Diagnosed or Responsive Multiple Myeloma

Study	N	Description of Patients	Regimen	Overall Response Rate (%) (%CR+%PR)	Median Event-Free Survival (months)	Median Overall Survival (months)	% Survival by years after treatment					Treatment Related Deaths (%)
							1	2	3	4	5	
Lenhoff et al. 2000 Non-randomized population-based study with historical controls; conducted by Nordic Myeloma Study Group at 14 centers	348 313	all myeloma patients registered for transplant protocol; n=274 transplanted; median age, 51 yr (all <60 yr); 70% stage III, 28% stage II historical controls from 5 earlier population-based studies at same centers; n=274 transplant-eligible median age, 54 years (all <60 yr); 56% stage III, 38% stage II	VAD induction, PBSC harvest after cyclophos-phamide+G-CSF; 200 mg/m^2 melphalan for conditioning no information provided	77 (34+43) not reported	27[a]/32[a] not reported	not reached (>60) p=0.001[a]/ 0.002[a] 39[a]/44[a]	86[a]/88[a] 82[a]/86[a]	76[a]/79[a] 67[a]/70[a]	66[a]/71[a] 53[a]/55[a]	55[a]/61[a] 43[a]/46[a]		(only one reported) no information provided
Fermand et al. 1995, 1998 Randomized comparison of immediate versus delayed transplant; conducted by Myélome Autogreffe Group	91 94	185 previously untreated pts with aggressive disease; age <56 yrs; randomized at diagnosis to up-front HDC + PBSC or to conventional chemotherapy with HDC + PBSC for salvage of primary resistance or relapsed disease (73 of 94 transplanted)	VAD (3 cycles) then HDC (CCNU/VP-16/ Cy/L-PAM) + TBI & PBSC then IFN VMCP & IFN maint with same HDC/PBSC for salvage	86 (19+67) 62 (6+56)	39 (95% CI: 29-48) 13 (95% CI: 9-18)	64.6 64		80 (72-88) 78 (70-86)	73 (64-82) 71 (62-80)	66 (56-76) 61 (51-71)		10 (in 1st year) 14
Barlogie et al. 1997, Jagannath et al. 1997 Non-randomized comparison of "total therapy" to SWOG historical controls	116 116	subset of 123 newly diagnosed patients with symptomatic myeloma; 50% age >50 yr; historical controls matched for age, β_2-microglobulin (β_2-M) & serum creatinine	VAD (X3); PBSC harvest after HD Cyclo + G-CSF; EDAP; up to 2X MEL200 + PBSC; IFN maint. VBMCP/VBAP or VAD	85 (40+45; by intent-to-treat, n=123) 52 (CR rate not available)	49 p=0.0001 22	not reached (>62) p=0.01 48			77 (EFS: 62) 65 (EFS: 30)	65 (EFS: 60) 50 (EFS: 25)	61 (EFS: 36) 39 (EFS: 19)	4 (in 1st year) not reported

[a] In each pair of numbers separated by a diagonal, the first number refers to the subgroup of patients who either received or were eligible for transplant, while the second number refers to the corresponding complete population.

The only other report that compared outcomes of HDC/AuSCS with outcomes of conventional therapy was a nonrandomized study of TanHDC/AuSCS conducted at the University of Arkansas (Barlogie et al. 1997; Jagannath et al. 1997). Matches were found for 116 of 123 newly diagnosed patients enrolled in a program of induction therapy, PBSC collection, and two planned cycles of HDC/AuSCS. Neither the mean nor the median age of this group was reported, although the authors indicated that 50% of the patients were older than 50 years. The 116 matched historical controls were enrolled in trials of conventional-dose combination chemotherapy conducted by the Southwest Oncology Group (SWOG). The differences in median event-free survival and overall survival were statistically significant, and favored the group given TanHDC/AuSCS (Table 1).

The IFM group has reported preliminary results from a randomized trial (IFM-94) that compared tandem HDC/AuSCS to single HDC/AuSCS in newly diagnosed patients with multiple myeloma (Attal et al. 1997b). Results from the first 100 patients per arm (half the patients enrolled) did not show a benefit of TanHDC/AuSCS relative to single HDC/AuSCS. Thus far, there has not been a final report from the IFM-94 trial.

Summary and Conclusions. Updated analyses from the IFM-90 trial confirm the conclusion of the earlier published report that there is a statistically and clinically significant improvement in outcomes after HDC/AuSCS, compared to conventional therapy. In addition, three comparative studies on HDC/AuSCS for treatment of newly diagnosed or responsive myeloma have been reported since completion of the 1996 TEC Assessment. Two non-randomized studies compared outcomes of HDC/AuSCS with outcomes of conventional-dose therapy. Results from these studies are consistent with the conclusion that HDC/AuSCS improves event-free and overall survival compared to conventional-dose therapy. The third study compared the outcomes of early HDC/AuSCS with those of conventional-dose induction therapy followed by late HDC/AuSCS for patients who relapse or have primary resistant disease. While there was no difference in overall survival, data suggested that early HDC/AuSCS was associated with a shorter period of chemotherapy and increased time without symptoms, treatment or toxicity. A high-priority trial sponsored by the National Cancer Institute (SWOG-9321/INT-0141) also is comparing outcomes of early HDC/AuSCS with those of conventional-dose induction followed by late HDC/AuSCS. This study was opened in 1996 and is expected to complete accrual this year (2000); however, no results have been reported.

B. In older patients with myeloma, does HDC/AuSCS improve health outcomes compared to conventional-dose treatment?

No randomized controlled trials compared outcomes of HDC/AuSCS with outcomes of conventional-dose therapy exclusively in older patients. Furthermore, no randomized controlled trial stratified patients by age prospectively and reported outcomes separately for older subgroups from the HDC/AuSCS and control arms. One non-randomized study directly compared outcomes for patients 55 years and older (Palumbo et al. 1999). Section A of Table 2 presents data from this study and from an unpublished analysis of subgroups aged ≥64 years from the same study (Boccadoro et al. 2000, unpublished data). Additional data are available from published studies and unpublished analyses on older and younger patients with myeloma

given HDC/AuSCS (Section B, Table 2) or conventional-dose therapy (Section C, Table 2). The data on older patients are used for indirect comparison to address question B.

1. Evidence for Direct Comparison of Outcomes

The only evidence for direct comparison of outcomes is from a trial reported by Palumbo et al. (1999). These investigators compared the outcomes of two or three cycles of HDC/AuSCS given to newly diagnosed myeloma patients to results of conventional dose melphalan and prednisone given to patients matched for age and serum β_2-microglobulin concentration (β_2-M). All of the patients had stage II (~25%) or III (~75%) disease. Three quarters of the patients in each arm were older than 60 years of age, with a median age of 64 years and an upper limit of 75 years in each arm. The 71 patients given HDC/AuSCS were treated from 1993 through 1997 while the 71 matched controls were treated from 1990 through 1995. Thus, this report used a mix of concurrent and historical controls, all meeting eligibility criteria of the HDC/AuSCS trial.

Note that the dose of melphalan used for myeloablative conditioning in the HDC/AuSCS arm was only 100 mg/m^2, half the dose used in most trials of HDC/AuSCS in younger patients. Furthermore, no radiation treatment or other drugs were used for conditioning. On the other hand, 96% of patients in the HDC/AuSCS arm received a second cycle of HDC/AuSCS and 55% received a third cycle after delays between cycles of approximately two months. Thus, the protocol required that sufficient CD34$^+$ PBSC be collected from all 71 patients to support three cycles of HDC/AuSCS.

Data abstracted from the report of Palumbo et al. (1999) included in Section A of Table 2 show greater rates of complete and overall response to therapy in the patients given HDC/AuSCS. The median duration of event-free survival (34 versus 18 months, $p<0.001$) and overall survival (>56 versus 48 months, $p<0.01$) was significantly longer in the HDC/AuSCS group than in the conventional-dose group. No early treatment-related deaths were reported in the group given HDC/AuSCS; the rate of early deaths was 4% in the group given melphalan plus prednisone.

An unpublished analysis on a subgroup (n=31) of patients aged ≥64 years from the study of Palumbo et al. (1999) also shows better outcomes with HDC/AuSCS (Boccadoro et al. 2000, unpublished data). For the patients given HDC/AuSCS, the medians and ranges for age and β_2-M levels and the distribution by stage of disease were indistinguishable from those of the matched control group (Section A, Table 2). The median duration of event-free survival (30.6 versus 17.8 months; $p<0.005$) and overall survival (56.5 versus 31.2 months; $p<0.01$) was significantly longer for the group given HDC/AuSCS.

Table 2. Studies with Data on Older Patients with Multiple Myeloma

Study	N	Description	Regimen	Overall Response Rate (%) (%CR/%PR)	Median Event-Free Survival (months)	Median Overall Survival (months)	% Survival by years after treatment					Treatment Related Deaths (%)
							1	2	3	4	5	
Section A: Direct Comparison of Outcomes of HDC/AuSCS to Outcomes of Conventional-dose Therapy in Older Patients												
Palumbo et al. 1999	71	newly diagnosed patients 55-75 yrs (median, 64; 75% >60 yr); 25% stage II, 75% stage III	2-3 cycles VAD, PBSC harvest after cyclo + G-CSF, 3X 100 mg/m^2	88 (47+41)	34	>56			91 (EFS: 45)	72 (EFS: 34)		0
Non-randomized trial on patients recruited 1993-97 with matched controls treated 1990-95	71	matched for β_2-M and age; 28% stage II, 72% stage III	melphalan then PBSC oral melphalan plus prednisone	49 (5+44)	17.7 p<0.001	48 p<0.01			67 (EFS: 28)	52 (EFS: 17)		4
Boccadoro et al. 2000	31	median age, 67 yrs (64-77); stage IIA, 29%; IIIA, 61%, IIIB, 10%; β_2-M, 3.5 mg/L (0.7 - 11.2)	2-3 cycles VAD, PBSC harvest after cyclo + G-CSF, 3X 100 mg/m^2		30.6	56.5	(EFS: 83)	84 (EFS: 64)	77 (EFS: 42)	62 (EFS: 33)	46 (EFS: 33)	
unpublished analysis on patients age ≥65 years from study of Palumbo et al. 1999	31	median age, 68 yrs (62-76); stage IIA, 26%; IIIA, 64%, IIIB, 10%; β_2-M, 3.4 mg/L (0.8 - 10.6)	melphalan then PBSC oral melphalan plus prednisone		17.8 p<0.005	31.2 p<0.01	(EFS: 77)	64 (EFS: 38)	43 (EFS: 22)	32 (EFS: 7)	24 (EFS: 0)	
Section B: Single-Arm Trials of HDC/AuSCS with Data Comparing Outcomes in Older and Younger Patients												
Guba et al. 1997; Siegel et al. 1999	49	age ≥65 yr (median, 67 yr; range, 65-76 yr); 2nd transplant in 65%	PBSC harvest after HD cyclo + G-CSF; 200 mg/m^2 MEL + PBSC; same regimen for 2nd transplant if ≥PR; for NR, 140 mg/m^2 MEL + (TBI or HD Cyclo)	CR: 20	18.0	39.6			58 (EFS: 37)	42 (EFS: 25)	42 (EFS: 25)	8
Tandem transplants; 43-45% > 1 yr prior therapy; retrospective comparison	49	age: median 52, range 37-64; matched for cytogenetics, β_2-M, CRP, albumin, and creatinine; 2nd transplant in 76%		CR: 43 P=0.02	33.6 p=0.2	57.6 p=0.4			60 (EFS: 47)	60 (EFS:22)	25 (EFS: 22)	2 p=0.2
Dumontet et al. 1998	20	age ≥60 yr; median 63, range 60-67; median 2 (2-4) previous regimens; 2nd transplant, 15%	100-200 mg/m^2 melphalan (median, 140) ± TBI then PBSC same regimens		12*							
	35	age <60 yr; median 50, range 26-59; median 2 (2-4) previous regimens; 2nd transplant, 34%			24*							
Barlogie and Tricot, unpublished data, 2000	39	age ≥65 yr (median, 68 yr; range, 65-76 yr); <8 mos. prior therapy; median β_2-M, 2.49 mg/L	enrolled in "Total Therapy" program (see Guba et al. 1997/Siegel et al. 1999) & received at least one cycle of high-dose therapy		32.6	54.5	84.6±0.06 (EFS: 72)	71.2±0.08 (EFS:58)	64.5±0.09 (EFS: 49)	52.9±0.12 (EFS: 32)	39.7±0.22 (EFS: 32)	
	342	age <65 yr (median, 50 yr; range, 14-64 yr); <8 mos. prior therapy; median β_2-M, 2.14 mg/L			32.8 p=0.57	72.2 p=0.46	87.4±0.02 (EFS: 79)	77.9±0.02 (EFS: 61)	67.0±0.03 (EFS: 47)	59.9±0.04 (EFS: 38)	53.3±0.05 (EFS: 33)	
ABMTR Statistical Center, 2000	165	median age, 63 yrs (61-72); 12.3 mos. (4-96) since diagnosis; stage I, 10%; II, 42%; III, 48%	all patients age ≥50 in registry database; trans-planted 1989-99; 136 centers		DFS: 8 (7-11)[a]	26 (20-38)[a]	74±8 (DFS:33)	56±10 (DFS: 12)	40±12 (DFS: 4)	23±13 (DFS: 1)	19±13 (DFS: 1)	5 ± 4
unpublished data	370	median age 55 yrs (50-60); 11.1 MOs (4-167) since diagnosis; stage I, 13%; II, 22%; III, 65%			DFS: 10 (8-12)[a]	41 (29-47)[a]	82±4 (DFS:41)	63±6 (DFS: 18)	52±7 (DFS: 7)	39±10 (DFS: 3)	28±13 (1)	8 ± 3

* median duration of freedom from progression (FFP)

[a] 95% confidence interval

Table 2 (continued). Studies with Data on Older Patients with Multiple Myeloma

Study	N	Description	Regimen	Overall Response Rate (%) (%CR/%PR)	Median Event-Free Survival (months)	Median Overall Survival (months)	% Survival by years after treatment					Treatment Related Deaths (%)
							1	2	3	4	5	
Section C: Trials of Conventional-Dose Regimens with Data on Outcomes in Older Patients												
Clavio et al. 1996 retrospective study; patients 65-74 yr compared to those >75	84	age 65-74 yr; 25% stage I; 33% stage II; 42% stage III; 60% with lytic bone lesions	melphalan + prednisone (73%) or combinations (27%)	69 (54+15) [OR+PR]		58			62	56	46	0 reported (9.5% grade 3-4 myelo-toxicity)
Bladé et al. 1996 PETHEMA randomized trial comparing MP to VCMP/VBAP	178	age ≥70 yr; similar to younger group in all other baseline parameters	melphalan+prednisone (51%) or VCMP/VBAP (49%)	54		23.4			35	22	13	8-9
Crowley (SWOG) unpublished data, 2000	373	age 65-74 yr (median, 69); no prior therapy; median β_2-M, 5.40 mg/L	patients in SWOG 8229 (VMCP/VBAP), SWOG 8624 (VAD or VMCP/ VBAP), or 9028 (VAD)		18 (prog.-free survival)	30.5	76.6±0.02 (PFS: 66)	57.2±0.03 (PFS: 42)	43.2±0.03 (PFS: 27)	31±0.02 (PFS: 18)	22.1±0.02 (PFS: 13)	
	723	age 28-64 yr (median, 57); no prior therapy; median β_2-M, 4.40			18	37.6	83.4±0.01 (PFS: 68)	65.3±0.02 (PFS: 41)	52.4±0.02 (PFS: 26)	39.5±0.02 (PFS: 19)	31.6±0.02 (PFS: 15)	

Summary, Direct Comparison. Only one non-randomized study permitted direct comparison of the health outcomes of HDC/AuSCS (n=71) with the health outcomes of conventional-dose therapy (n=71) in older patients (Palumbo et al. 1999). The most relevant data are from an unpublished subgroup analysis restricted to the 31 patients in each treatment arm, age ≥64 years (Boccadoro et al. 2000, unpublished data). Results from this analysis support the conclusion that HDC/AuSCS improves health outcomes compared to those of conventional-dose treatment in older patients with myeloma. However, several factors may weaken the evidence provided by this study. First, lower doses of myeloablative conditioning chemotherapy were used for HDC/AuSCS than are used most commonly in other studies. Second, 25% of the patients included in each arm of the full study were less than 60 years of age and a subgroup analysis was needed to obtain data on patients aged ≥64 years. Although subgroup analyses are useful for generating hypotheses, they are rarely conclusive unless patients are prospectively stratified. Third, this was not a randomized study, β_2-M was the only prognostic factor besides age that was used to select matched patients for the control group, and the distribution by stage of disease was the only other prognostic information provided.

2. Evidence for Indirect Comparison of Outcomes

Evidence was available from two published studies and two unpublished analyses that reported outcomes separately for older and younger patients given HDC/AuSCS for myeloma (Section B, Table 2). Evidence for indirect comparison with these data on HDC/AuSCS was available from two published studies and one unpublished analysis that reported outcomes separately for subgroups of older and younger patients from trials of conventional-dose therapy (Section C, Table 2). Only the data on older patients from each group of studies are used for this indirect comparison.

Outcomes of HDC/AuSCS. Barlogie and his colleagues at the University of Arkansas published two reports that compare results for older and younger patients treated in their tandem transplant program (Guba et al. 1997; Siegel et al. 1999). In the University of Arkansas tandem transplant program, patients are conditioned with 200 mg/m^2 melphalan in the first cycle. In the second cycle, they receive the same dose of melphalan if they have achieved at least a partial remission. The regimen in the second cycle uses a lower dose of melphalan (140 mg/m^2) plus either total body irradiation or cyclophosphamide (6 g/m^2) for those without at least a partial remission after the first cycle. Hematopoietic function is restored after each cycle by infusion of PBSC harvested prior to the first cycle.

The first report from the Arkansas group (Guba et al. 1997) analyzed all patients who had undergone PBSC mobilization in the tandem transplant protocol (n=225). The analysis compared 57 patients aged ≥60 years to 168 patients aged less than 60 years. Since patients ≥65 years old from this study also are included in the second paper, only the data from the later report are shown in Table 2 (Siegel et al. 1999). In the second report, the Arkansas group compared outcomes (at a minimum follow-up of 18 months post transplant) for 49 patients aged ≥65 years, to outcomes for 49 patients aged less than 65 years matched for five prognostic factors (see Section B, Table 2). For the older patients, the median duration of event-free survival was 18 months and the median duration of overall survival was 39.6 months. Kaplan-Meier analysis

projected that event-free (25%) and overall survival (42%) remained constant between 4 and 5 years after the first transplant. Transplant-related mortality was 8% in the older patients.

In both of the published reports, a substantial percentage of patients either had resistant disease (30% to 45%) or had received >1 year of previous therapy (30% to 46%) (Guba et al. 1997; Siegel et al. 1999). Drs. Barlogie and Tricot provided an unpublished analysis of patients with less than 8 months of prior therapy that compared outcomes of HDC/AuSCS for 39 patients aged ≥65 (up to 76 years) to those for 342 patients less than 65 years (Section B of Table 2, unpublished data, 2000). For the older patients, median event-free survival was 32.6 months and overall survival was 54.5 months. At four years, event-free survival was 32%, and overall survival was 53%. Data on transplant-related mortality were not provided.

The Statistical Center of the Autologous Blood and Marrow Transplant Registry (ABMTR; Milwaukee, WI) provided additional unpublished data from an analysis that compared older and younger patients. For 165 patients ≥60 years old, the median duration of overall survival was 26 months (95% CI, 20-38 months) and the median duration of disease-free survival was 8 months (95% CI, 7-11 months). Overall survival at 4 years was 23%, and disease-free survival at 4 years was 1%. Transplant-related mortality was 5±4%.

Only one other published study reported on outcomes of HDC/AuSCS in older patients (Dumontet et al. 1998). A report from this single-arm trial compared 20 patients aged ≥60 years with 35 patients aged less than 60 years. Patients were given one or two cycles high-dose melphalan (100-200 mg/m^2) with or without total body irradiation, followed by hematopoietic rescue with PBSC. In the older patient group, 15% of patients received a second transplant. The only outcome reported separately for the two age groups was the median duration of freedom from progression (FFP), which was 12 months in the older group.

Outcomes of Conventional-Dose Therapy. The literature search identified two recent reports that reported outcomes for older myeloma patients managed with conventional-dose therapy (Section C, Table 2). Clavio et al. (1996) compared outcomes reported for 84 patients whose age ranged from 65 to 74 years with outcomes reported for 29 patients aged ≥75 years. However, no data were reported on outcomes in patients less than 65 years of age. Patients were treated with melphalan plus prednisone (74%) or with combination regimens (26%).

Only the data on patients aged 65-74 are shown in Table 2 and used here for indirect comparison, since the oldest patients included in trials of HDC/AuSCS were 76 years of age. For these patients, Clavio et al. (1996) reported that the median duration of survival was 58 months (measured from diagnosis) and estimated that percent survival at four and five years after treatment were 56% and 46%, respectively. However, 25% of the myeloma patients in this study were in stage I and only 42% were in stage III. Consequently, results reported for these patients may not be comparable with those from studies of HDC/AuSCS, in which few or no patients were in stage I and 60% to 75% were in stage III. No treatment-related mortality was reported for the 84 patients aged 65 to 74 years treated by Clavio et al. (1996).

Investigators from Spain compared outcomes for 178 myeloma patients aged ≥70 to outcomes for 309 patients less than 70 years of age (Bladé et al. 1996). These data were from a

randomized trial comparing the outcomes of treatment with melphalan plus prednisone to the outcomes of alternating cycles of two combination regimens (VCMP/VBAP). The median duration of overall survival was 23.4 months for the patients aged ≥70 years. Estimates of the percent survival at four and five years were 22% and 13%, respectively. Treatment-related mortality was 8% to 9%. However, no information was available on the upper limit of the age range for the patients aged ≥70 years. Therefore, the comparability of these patients with the older patients given HDC/AuSCS cannot be evaluated.

In addition to the published data, the Southwest Oncology Group has provided an unpublished analysis of data from trials that investigated conventional-dose therapy for myeloma (SWOG 2000, unpublished data). These patients were enrolled in three randomized trials that compared different regimens of conventional-dose induction therapy and/or different strategies for consolidation or maintenance therapy after remission induction. SWOG 8229 compared different alternating cycles of VMCP and VBAP, and also tested the value of hemibody irradiation for consolidation (Salmon et al. 1990). SWOG 8624 compared VAD to VMCP/ VBAP (with or without alternate-day prednisone between cycles) and also tested the use of interferon for maintenance (Salmon et al. 1994). SWOG 9028 compared VAD alone to VAD plus the chemosensitizers verapamil and quinine, and also compare interferon alone to interferon plus prednisone for maintenance therapy (Salmon et al. 1998).

Among over 1,200 patients enrolled in these trials, 373 were from 65 to 74 years of age and 723 were aged less than 65 years. In the group aged 65 to 74, median overall survival was 30.5 months and median progression-free survival was 18 months. The probability of overall survival at 4 and 5 years after treatment was 31% and 22%, respectively. The probability of progression-free survival at 4 and 5 years was 18% and 13%, respectively.

Summary, Indirect Comparisons. No study has been published that directly compares outcomes of HDC/AuSCS with outcomes of conventional therapy in older myeloma patients. Published data on the outcomes of HDC/AuSCS in older patients (n=49; age 65–76) were available from a single-arm study of tandem transplants (Guba et al. 1997; Siegel et al. 1999). These were supplemented with two unpublished analyses. The first included 39 patients ≥65 years of age enrolled in the tandem transplant program after less than 8 months of previous therapy (Barlogie 1999, unpublished data). The second included 165 patients >60 years of age with non-progressive disease at transplant (ABMTR Statistical Center 2000, unpublished data). Data on the outcomes of conventional-dose therapy in older patients were available from two published reports on conventional-dose therapy in older patients (Clavio et al. 1996; Bladé et al. 1996) and from an unpublished analysis of data provided by the Southwest Oncology Group (Crowley 2000).

Outcomes of tandem transplants in patients ≥65 years of age were nearly the same as the outcomes of conventional therapy in 84 patients age ranged from 65 to 74 (Clavio et al. 1996). Outcomes for the older patients given tandem transplants were slightly better than the outcomes of conventional-dose therapy in 178 patient aged ≥70 (Bladé et al. 1996) and the 646 patients aged 65 to 74 given conventional-dose therapy in trials conducted by the Southwest Oncology Group. However, outcomes for the 165 transplanted patients aged >60 years reported to the ABMTR Statistical Center were slightly worse than those reported by Bladé et al. (1996) and in

the SWOG unpublished analysis for older patients given conventional-dose therapy. The outcomes for older patients reported to the ABMTR were substantially worse than those reported by Clavio et al. (1996) after conventional-dose treatment.

Patients enrolled in a clinical protocol such as the "total therapy" program of Barlogie and colleagues usually must meet relatively strict eligibility criteria. Those reported to the ABMTR Statistical Center by 136 different transplant teams in North and South America may represent a broader distribution with respect to prior treatment history, comorbidities, general health status, and critical parameters of organ function. The only baseline characteristic that can be compared for these two groups of older patients given HDC/AuSCS is the median interval from diagnosis to transplant. It was 12.3 months (range, 4-96 months) for the 165 patients in the ABMTR database, while the University of Arkansas analysis was limited to patients with less than 8 months of prior therapy.

Assuming that differences in patient selection explain the differences in outcome, this evidence appears to suggest that HDC/AuSCS may improve health outcomes for carefully selected older patients with myeloma, when compared with conventional-dose therapy. However, the evidence also suggests that outcomes of HDC/AuSCS may be worse than the outcomes of conventional-dose therapy if stringent patient selection criteria are relaxed. Note also that differences between the patients given HDC/AuSCS and those managed conventionally with respect to age ranges, stage distributions, and a variety of other prognostic factors weaken the validity of an indirect comparison of outcomes across these studies.

Overall Conclusion: HDC/AuSCS versus Conventional-Dose Therapy in Older Patients

One non-randomized study permitted direct comparison of the health outcomes of HDC/AuSCS (n=71) with the health outcomes of conventional-dose therapy (n=71) in older patients (Palumbo et al. 1999). The most relevant data are from an unpublished subgroup analysis restricted to the 31 patients in each treatment arm, age ≥64 years (Boccadoro et al. 2000, unpublished data). From the limited evidence provided by this analysis, the outcomes of HDC/AuSCS appear to be superior to the outcomes of conventional-dose treatment for myeloma in older patients.

Table 3 summarizes the available data directly and indirectly comparing the outcomes of HDC/AuSCS with those of conventional-dose therapy in older myeloma patients (mid-sixties to mid-seventies). For each outcome, the table lists the range of results across all studies reporting on this age group, with the number of patients and the number of studies in parentheses. Except for the data from the ABMTR Statistical Center (shown separately in brackets), the median duration of event-free survival and overall survival in older myeloma patients appears longer after HDC/AuSCS than after conventional-dose therapy. With the same exception, the percent event-free survival and overall survival at 4 years after treatment of older patients with myeloma appears greater for those given HDC/AuSCS than for those treated conventionally. HDC/AuSCS does not appear to result in greater treatment-related mortality than is reported after conventional-dose therapy.

There are plausible reasons to explain why the data on patients older than 60 years of age from the ABMTR Statistical Center varies from that reported in other studies. It is likely that these

patients, who were treated by 136 separate transplant teams, are the least homogeneous and least stringently selected group of patients among the available studies.

Taken together, the data in Table 3 suggest that HDC/AuSCS might improve the health outcomes of carefully selected older myeloma patients, when compared with those of conventional-dose therapy. However, the generalizability of this conclusion is weakened by the use of a lower intensity conditioning regimen for HDC/AuSCS in the only study that permitted direct comparison of outcomes. Transplant-related mortality might be higher in older patients given more intensive conditioning regimens. The validity and generalizability of these conclusions also are weakened by possible differences between the patient groups treated in the two sets of studies used for indirect comparison that impair the comparability of their results.

Nevertheless, based on the evidence reviewed for this assessment, it appears more likely than not that for multiple myeloma patients in the young-old age range (mid-sixties to mid-seventies) without contraindications to the treatment, HDC/AuSCS improves outcomes when compared with the outcomes of conventional-dose therapy. Although direct evidence on this question is limited, the consistent observations in studies of all age ranges, and the indirect comparison of outcomes for older age groups makes it likely that the improvement in outcomes seen in the younger group extends to otherwise-similar patients in the older group. Consequently, there appears to be no rationale to establish an inflexible age cut-off for this treatment within the young-old age range.

Table 3: Summary of Outcomes Reported for HDC/AuSCS and Conventional-Dose Therapy in Older Patients with Multiple Myeloma

Outcome	Older Patients Given HDC/AuSCS	Older Patients Treated with Conventional Doses
Median EFS, DFS or PFS	[8] 12–34 months (n=305; 4 studies)	18 months (n=444; 2 studies)
EFS, DFS or PFS at 4 years	[1%] 25–34% (n=285; 3 studies)	17–18% (n=444; 2 studies)
Median overall survival	[26] 40–55 months (n=285; 3 studies)	30–58 months (n=801; 3 studies)
Survival at 4 years	[23%] 42–72% (n=285; 3 studies)	31–56% (n=801; 3 studies)
Treatment-related mortality	[5%] 0–8% (n=285; 3 studies)	0–4% (n=155; 2 studies)

C. Do older patients with myeloma obtain a benefit from HDC/AuSCS that is similar to that obtained by younger patients?

Two published studies (Guba et al. 1997/Siegel et al. 1999; Dumontet et al. 1998) and two unpublished analyses (Barlogie and Tricot 2000; ABMTR Statistical Center 2000) provide data to compare directly older and younger patients with respect to the outcomes of HDC/AuSCS as therapy for myeloma. One report also provides data to compare stem-cell mobilization and harvest in older and younger myeloma patients (Guba et al. 1997).

Guba et al. (1997) analyzed patients enrolled in the University of Arkansas tandem transplant protocol who had undergone PBSC mobilization (n=225). The analysis compared 57 patients aged ≥60 years to 168 patients aged less than 60 years. They compared the yield of stem cells (an outcome not included in Table 2) as a function of age for patient groups with equivalent durations of previous therapy. For those with ≤12 months prior therapy, the median numbers of $CD34^+$ stem cells were 12 (range 7–22), 10 (range 6-18), and 10 (range 6-20) x 10^6/kg, respectively, for groups aged less than 50 (n=57), 50–59 (n=38), and ≥60 years (n=31). Additionally, the medians for PBSC yield were equivalent and the ranges overlapped when the same three age groups were compared for patients with 13–24 months or with >24 months prior therapy. There were also no statistically or clinically significant differences in the median time from transplant to recovery of neutrophil counts (11 days for each group) or the median time to recovery of platelet counts (12, 13, and 14 days, respectively).

The data of Guba et al. (1997) demonstrate that it is feasible to safely and effectively mobilize, harvest, and transplant PBSC in some patients older than 60 years. However, 43 additional patients aged ≥60 years were evaluated for transplant but did not undergo stem-cell mobilization and harvest because of poor performance status or inadequate cardiopulmonary or renal function. Thus, it is likely that patient selection plays a critical role in the feasibility of autologous stem-cell support for older patients, as well as in the overall outcomes of their treatment with HDC/AuSCS.

Guba et al. (1997) reported that the median duration of event-free survival after transplant was longer in younger patients than in older patients (24 versus >40 months; p=0.006). There was also a trend towards increased overall survival for the younger patients (>40 versus >35 months; p=0.06). Because patients from this report >64 years of age also were included in the subsequent report (Siegel et al. 1999), these outcomes were omitted from Table 2.

The second report from the Arkansas group (Siegel et al. 1999) was an analysis of 49 patients ≥65 and an equivalent number less than 65 years old, all of whom were enrolled in the tandem transplant protocol and had ≥18 months of follow-up. Younger patients were selected from a total of 501 as controls by matching for five prognostic factors other than age (see Section B, Table 2). Based on earlier studies of hematopoietic recovery as a function of the number of stem cells infused, the tandem transplant protocol prospectively specified the harvest of ≥5 x 10^6/kg $CD34^+$ stem cells as sufficient to support two cycles of HDC/AuSCS. The required minimum cell number was harvested from 73% of the older patients and 83% of the matched younger patients (p=0.2). Although the differences were not statistically significant, the median duration of both event free survival (18.0 months versus 33.6 months; p=0.2) and overall survival (39.6 months versus 57.6 months; p=0.4) was shorter for the older patients. Transplant related mortality was 8% for the older patients and 2% for the younger patients.

Dumontet et al. (1998) compared 20 patients aged ≥60 years with 35 patients less than 60 years old with respect to the median duration of freedom from progression (FFP) after HDC/AuSCS. Older patients were free from progression for 12 months while younger patients were free from progression for 24 months. FFP was the only outcome compared for the older and younger subgroups in this study

An unpublished analysis by the University of Arkansas group compared event-free survival and overall survival after tandem transplants for myeloma in 39 patients aged ≥65 years to 342 patients aged less than 65 years. All patients in both groups had less than 8 months of prior therapy. The median serum concentration of β_2-M was slightly higher in the older patients (2.49 versus 2.14 mg/L; p=0.05), but the two groups were quite similar with respect to other baseline characteristics including creatinine clearance (p=0.47), hemoglobin levels (p=0.81), LDH levels (p=0.21), C-reactive protein (p=0.95), and the absence of unfavorable cytogentic abnormalities (p=0.97). There were no statistically significant differences between the two age groups with respect to median event-free survival (32.6 versus 32.8 months, p=0.57) or overall survival (54.5 versus 72.2 months; p=0.46).

A second unpublished analysis from the University of Arkansas, without limits on the duration of prior therapy, compared 104 older patients with 848 younger patients. Survival curves were compared separately for subgroups of the older and younger patients with high, intermediate, and low-risk disease defined by β_2-M levels and cytogenetics. For each risk group, the survival curves for older and younger patients were superimposable (p=0.6 to p=0.9). In addition, the event-free survival (p=0.5) and overall survival (p=0.9) curves for older and younger patients with myeloma were superimposable for subgroups with ≤12 months of therapy prior to enrollment in the tandem transplant trials. However, no estimates of median survival or event-free survival were provided with this analysis. In addition, both the older and younger groups included patients with refractory disease. Therefore, these data were omitted from Table 2.

Another unpublished analysis from the ABMTR Statistical Center (2000) compared outcomes of HDC/AuSCS in 165 patients aged >60 years with outcomes in 370 patients between 50 and 60 years old. Data included in Table 2 show that the two age groups were similar with respect to the median interval from diagnosis to transplant and the distribution by stage of disease at diagnosis. Additional data demonstrate that the two groups also were similar with respect to disease status at transplant (26–27% complete remission, 68–69% partial remission, 5% stable disease), percentage of male patients (61–62%), the conditioning regimens used (not shown), and the year of transplant (78% versus 87% transplanted since 1995). However, information was unavailable on several other important prognostic variables, such as β_2-M, C-reactive protein, or creatinine levels.

The median duration of survival appeared to be greater in the younger group of patients reported to the ABMTR (41 versus 26 months). However, there was substantial overlap between the 95% confidence intervals for the two groups (29-47 months versus 20-38 months). There was no apparent difference between the two age groups with respect to the duration of disease-free survival (8-12 months versus 7-11 months). Transplant-related mortality also appeared to be about the same in each group (8±3% versus 5±4%).

Summary and Conclusion. Table 4 summarizes data from the studies included in Table 2 on the outcomes of HDC/AuSCS in older and younger patients with multiple myeloma. For younger patients, the data in Table 4 also includes evidence from controlled studies reviewed in the previous TEC Assessment (BCBSA 1996) as well as all new evidence summarized in Table 1 of this assessment. For each outcome, the table lists the range of results across all studies reporting

outcomes for this age range, with the number of patients and the number of studies in parentheses.

For purposes of this comparison, studies on older patients with multiple myeloma are those that reported outcomes for patient groups older than 60 years of age. Note that the oldest patients included in these studies were 76 years of age, and most of the studies excluded patients with poor performance status or severe comorbid conditions. The data summarized in Table 4 show that in some studies, the median duration of event-free and overall survival after HDC/AuSCS for older patients with myeloma is somewhat shorter than the lower limit of the range reported for the same outcome after HDC/AuSCS in younger patients. Survival at 4 years after HDC/AuSCS also appears somewhat shorter in older than in younger patients. Treatment related mortality does not appear to be greater among older patients (up to age 76 and in good health except for their myeloma) than among their younger counterparts.

The comparison of data on overall survival suggests that health outcomes of HDC/AuSCS in older patients may be slightly inferior to those in younger patients. However, this may reflect the patients' age more than it does differences in the safety and effectiveness of HDC/AuSCS. Two of the four analyses that permit direct comparison of outcomes (Barlogie and Tricot 2000; ABMTR Statistical Center 2000) show equivalent event-free survival after HDC/AuSCS in older and younger patients, although overall survival was longer in the younger patients.

Table 4: Summary of Outcomes Reported for HDC/AuSCS in Younger and Older Patients with Multiple Myeloma

Outcome	Younger Patients Given HDC/AuSCS	Older Patients Given HDC/AuSCS
Median EFS, DFS or PFS	10–49 months[a] (n=1,109; 7 studies)	8–34 months (n=305; 4 studies)
EFS, DFS or PFS at 4 years	3%, 38% (n=712; 2 studies)	1–34% (n=285; 3 studies)
Median overall survival	41–72 months[a] (n=1,070; 6 studies)	26–55 months (n=285; 3 studies)
Survival at 4 years	39–71%[a] (n=1,070; 6 studies)	26–72% (n=285; 3 studies)
Treatment-related mortality	4–11%[a] (n=722; 5 studies)	0–8% (n=285; 3 studies)

[a] Includes data from an earlier TEC Assessment (BCBSA, 1996) not in Table 2 of this assessment.

ASSESSMENT CONCLUSIONS

A. Does recent evidence from comparative studies confirm the earlier conclusion that HDC/AuSCS improves health outcomes in younger patients with multiple myeloma?

Updated data from the only randomized trial comparing HDC/AuSCS with conventional-dose therapy in patients with myeloma and results of other studies published since its completion are consistent with the conclusion that HDC/AuSCS improves event-free and overall survival compared to conventional-dose therapy.

B. In older patients with myeloma, does HDC/AuSCS improve health outcomes compared to conventional-dose treatment?

Based on the evidence reviewed for this technology assessment, it appears more likely than not that for multiple myeloma patients in the young-old age range (mid-sixties to mid-seventies) without contra-indications to the treatment, HDC/AuSCS improves outcomes when compared with the outcomes of conventional-dose therapy. Although direct evidence on this question is limited, the consistent observations in studies of all age ranges, and the indirect comparison of outcomes for older age groups makes it likely that the improvement in outcomes seen in the younger group extends to otherwise similar patients in the older group.

C. Do older patients with myeloma obtain a benefit from HDC/AuSCS that is similar to that obtained by younger patients?

The duration of overall survival after HDC/AuSCS in older patients appears to be slightly shorter than in younger patients. However, this may reflect the patients' age more than it does differences in the safety and effectiveness of HDC/AuSCS. In 2 of the 4 analyses that permit direct comparison of outcomes, the duration of event-free survival after HDC/AuSCS is equivalent in older and younger patients, although overall survival was longer in the younger patients.

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